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L1      43460 PROTEOGLYCAN

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L2       6008 L1 (3A) SYNTHE?

=> s l1 (3a) produc?
L3       1141 L1 (3A) PRODUC?

=> l2 or l3
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For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l2 or l3
L4       6820 L2 OR L3

=> s l4 and (osteoinduc? or BMP or LIM)
L5        104 L4 AND (OSTEOINDUC? OR BMP OR LIM)

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6         56 DUP REM L5 (48 DUPLICATES REMOVED)

=> d bib abs 1-
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L6  ANSWER 1 OF 56  CAPLUS  COPYRIGHT 2007 ACS on STN
AN  2007:647198  CAPLUS <<LOGINID::20071022>>
DN  147:65618
TI  Inducing bone mineralization by expression of the  ***LIM***
    mineralization protein gene to induce aggrecan biosynthesis
IN  McKay, William F.; Boden, Scott D.; Yoon, Sangwook T.
PA  USA
SO  U.S. Pat. Appl. Publ., 91pp., Cont.-in-part of U.S. Ser. No. 382,844.
    CODEN: USXXCO
DT  Patent
LA  English
FAN.CNT 4
    PATENT NO.          KIND  DATE      APPLICATION NO.     DATE
    ------------------  ----  --------  ------------------  --------
PI  US 2007134218       A1    20070614  US 2006-602805      20061121
    US 2003180266       A1    20030925  US 2002-292951      20021113
    US 2003225021       A1    20031204  US 2003-382844      20030307
    ZA 2004003714       A     20060222  ZA 2004-3714        20040514
PRAI US 2001-331321P    P     20011114
    US 2002-292951      A2    20021113
    US 2003-382844      A2    20030307
    US 1988-124238      A     19880729
    US 2000-959578      A     20000428
AB  Methods of increasing the levels of a proteoglycan such as aggrecan in a
    cell to promote bone mineralization are described. These methods involve
    increasing the levels of  ***LIM***  domain-contg. mineralization
    protein-1 (LMP-1), typically by introduction of an expression cassette for
    the protein gene. The expression cassette may be delivered as naked DNA,
    such as a plasmid, or using a viral system. The method can be used to
    induce  ***proteoglycan***  ***synthesis***  in osseous cells or to
    stimulate proteoglycan or collagen biosynthesis in cells such as
    intervertebral disk cells including cells of the nucleus pulposus and
    annulus fibrosus. Antsisense knockdown of LMP-1 gene expression in
    osteoblasts prevented mineral nodule formation and osteocalcin secretion.
    CDNAs for  ***LIM***  proteins functional in membranous bone formation
    (designated LMP-1) were cloned and sequenced from rat osteoblasts and
    human cDNA libraries. Human LMP has several splicing isoforms and the
    gene encoding human LMP-1 was sequenced. Methods of expressing the
     ***LIM***  mineralization protein gene and assessing glycosylation of the
     ***LIM***  mineralization protein in prokaryotic and non-mammalian
    eukaryotic cells are also described. Transfection with an adenoviral
    vector expressing human LMP-1 is effective in increasing
     ***proteoglycan***  ***synthesis***  of intervertebral disk cells.
    The dose of virus leading to the highest transgene expression (MOI 1000)
    also leads to the highest induction of sol. glycosaminoglycans, suggesting
    a correlation between LMP-1 levels and sol. glycosaminoglycan
    biosynthesis. These data indicate that hLMP-1 gene therapy is a method of
    increasing  ***proteoglycan***  ***synthesis***  in the
    intervertebral disk, and that hLMP-1 is an agent for treating disk
    disease.

L6  ANSWER 2 OF 56  CAPLUS  COPYRIGHT 2007 ACS on STN
AN  2007:486422  CAPLUS <<LOGINID::20071022>>
DN  146:476694
TI  Expression of  ***LIM***  mineralization protein in mammalian cells for
    gene therapy of bone formation
IN  Boden, Scott D.; Sangadala, Sreedhara; Titus, F. Louisa; McKay, William F.
PA  USA
```

SO U.S. Pat. Appl. Publ., 70pp., Cont.-in-part of U.S. Ser. No. 292,951.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2007099176	A1	20070503	US 2006-545349	20061010
US 2003180266	A1	20030925	US 2002-292951	20021113
CN 1665391	A	20050907	CN 2002-827099	20021114
ZA 2004003714	A	20060222	ZA 2004-3714	20040514
PRAI US 2001-331321P	P	20011114		
US 2002-292951	A2	20021113		
US 1988-124238	A	19880729		
US 2000-959578	A	20000428		

AB ***LIM*** domain-contg. proteins involved in bone formation and methods of expressing ***LIM*** mineralization protein in mammalian cells are described. ***LIM*** proteins functional in membraneous bone formation (designated LMP-1) are cloned and sequenced from rat osteoblasts and human cDNA libraries; human LMP exists as several spliced isoforms and the genomic sequence encoding human LMP-1 was detd. Methods of expressing ***LIM*** mineralization protein and assessing glycosylation of the ***LIM*** mineralization protein in prokaryotic and non-mammalian eukaryotic cells are also described. The methods involve transfecting the cells with an isolated nucleic acid comprising a nucleotide sequence encoding a ***LIM*** mineralization protein (LMP). Transfection may be accomplished in vitro, ex vivo or in vivo by direct injection of virus or naked DNA, or by a nonviral vector such as a plasmid. Transfection with an adenoviral vector expressing human LMP-1 is effective in increasing ***proteoglycan*** ***synthesis*** of intervertebral disk cells. The dose of virus leading to the highest transgene expression (MOI 1000) also leads to the highest induction of sol. glycosaminoglycans, suggesting a correlation between hLMP-1 expression and sol. glycosaminoglycan induction. These data indicate that hLMP-1 gene therapy is a method of increasing ***proteoglycan*** ***synthesis*** in the intervertebral disk, and that hLMP-1 is an agent for treating disk disease.

L6 ANSWER 3 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
DUPLICATE 1
AN 2007:439063 BIOSIS <<LOGINID::20071022>>
DN PREV200700428875
TI Toll-like receptors and chondrocytes - The lipopolysaccharide-induced decrease in cartilage matrix synthesis is dependent on the presence of Toll-like receptor 4 and antagonized by bone morphogenetic protein 7.
AU Bobacz, K. [Reprint Author]; Sunk, I. G.; Hofstaetter, J. G.; Amoyo, L.; Toma, C. D.; Akira, S.; Weichhart, T.; Saemann, M.; Smolen, J. S.
CS Allgemeines Krankenhaus Wien, Dept Internal Med 3, Div Rheumatol, Waehringer Guertel 18-20, A-1090 Vienna, Austria
klaus.bobacz@meduniwien.ac.at
SO Arthritis & Rheumatism, (JUN 2007) Vol. 56, No. 6, pp. 1880-1893.
CODEN: ARHEAW. ISSN: 0004-3591.
DT Article
LA English
ED Entered STN: 15 Aug 2007
Last Updated on STN: 15 Aug 2007
AB Objective. To assess the presence of Toll-like receptors (TLRs) 1-9 in human articular cartilage, and to investigate the effects of lipopolysaccharide (LPS)induced activation of TLR-4 on biosyntlietic activity and matrix production by human articular chondrocytes.Methods. TLRs 1-9 were assessed in human articular cartilage by reverse transcription-polymerase chain reaction (RT-PCR); TLR-4 was also analyzed by Western blotting and immunohistochemistry. Articular chondrocytes were isolated from human donors and from wild-type or TLR-4(-/-) mice. Chondrocyte monolayer cultures were incubated with interieukin-1 beta (IL-1 beta) and LPS in the absence or presence of bone morphogenetic protein 7 (***BMP*** -7) and IL-1 receptor antagonist (IL-IRa). Neosynthesis of sulfated glycosaminoglycans (sGAG) was measured by S-35-sulfate incorporation. Endogenous gene expression of cartilage markers as well as IL-1,6 was examined using RT-PCR. The involvement of p38 kinase or p44/42 kinase (ERK-1/2) in LPS-mediated TLR-4 signaling was investigated by immunoblotting, RT-PCR, and sGAG synthesis.Results. TLRs 1-9 were found on the messenger RNA (mRNA) level in human articular chondrocytes. The presence of TLR-4 was also observed on the protein level. In murine and human articular chondrocytes, but not in chondrocytes derived from TLR-4(-/-) mice, stimulation with LPS resulted in a decrease in total ***proteoglycan*** ***synthesis*** . IL-1 beta mRNA expression was increased by TLR-4 activation, whereas expression of aggrecan and type 11 collagen was significantly decreased. The presence of ***BMP*** -7 and IL-1Ra antagonized the anti-anabolic effects of LPS. Blocking of p38, but not ERK-1/2, resulted in inhibition of both LPS-mediated IL-1 beta gene expression and the negative effects of LPS on matrix biosynthesis.Conclusion. These data demonstrate the presence of TLRs in human articular cartilage. The suppressive effects of LPS on cartilage biosynthetic activity are dependent on the presence of TLR-4, are governed, at least in part, by an up-regulation of IL-1 beta, and are mediated by p38 kinase. These in vitro data indicate an anti-anabolic effect of TLR-4 in articular chondrocytes that may hamper cartilage repair in various joint diseases.

L6 ANSWER 4 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2007148751 EMBASE <<LOGINID::20071022>>
TI Increased accumulation of superficial zone protein (SZF) in articular cartilage in response to bone morphogenetic protein-7 and growth factors.
AU Khalafi A.; Schmid T.M.; Neu C.; Reddi A.H.
CS A. Khalafi, Center for Tissue Regeneration and Repair, Department of Orthopaedic Surgery, University of California-Davis, Sacramento, CA 95817, United States. afshin.khalafi@ucdmc.ucdavis.edu
SO Journal of Orthopaedic Research, (Mar 2007) Vol. 25, No. 3, pp. 293-303.
Refs: 56
ISSN: 0736-0266 CODEN: JOREDR
CY United States
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry
033 Orthopedic Surgery
LA English
SL English
ED Entered STN: 25 Apr 2007
Last Updated on STN: 25 Apr 2007
AB The purpose of this study was to investigate the role of bone morphogenetic proteins (BMPs), such as ***BMP*** -7, growth factors, and cytokines, in the accumulation of superficial zone protein (SZP) in bovine articular cartilage. Calf superficial articular cartilage discs and chondrocytes were obtained for explant and monolayer culture systems, respectively. Dose- and time-dependent actions of ***BMP*** -7 on SZP accumulation were investigated in both explant and monolayer culture systems. In addition, actions of various morphogens and growth factors [***BMP*** -2, ***BMP*** -4, fibroblast growth factor 2 (FGF-2), insulin-like growth factor 1(IGF-1), platelet-derived growth factor (PDGF), and transforming growth factor .beta. (TGF-.beta.1)], and cytokines [interleukin (IL)-l.alpha., IL-1.beta., and tumor necrosis factor (TNF-.alpha.)] alone, and in combination with ***BMP*** -7, on SZP accumulation were investigated in monolayer culture systems. SZP accumulation was quantified in both the cartilage and the medium using SDS-PAGE and subsequent immunoblotting. In both explant and monolayer cultures, ***BMP*** -7 increased SZP accumulation in a dose- and time-dependent fashion ($p < 0.05$). Furthermore, SZP accumulation was significantly increased in monolayer cultures by FGF-2, IGF-1, PDGF, and TGF-.beta.1 ($p < 0.05$). Both IL-l.alpha. and TNF-.alpha. significantly reduced SZP accumulation ($p < 0.05$). The inhibition of SZP accumulation by TNF-.alpha. was partially alleviated by concurrent treatment with ***BMP*** -7. The results of this investigation provide novel insights into the role of morphogens, especially ***BMP*** -7, growth factors, and cytokines in the accumulation of SZP in articular cartilage. This information has clinical implications because stimulation of SZP may ameliorate the pathology of joint function in arthritis. Furthermore, tissue engineering approaches to articular cartilage may depend on the optimal synthesis and assembly of SZP in the superficial zone to ensure functional tissue architecture. .COPYRGT. 2006 Orthopaedic Research Society. Published by Wiley Periodicals, Inc.

L6 ANSWER 5 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
DUPLICATE 2
AN 2006:549018 BIOSIS <<LOGINID::20071022>>
DN PREV200600549037
TI Comparative effects of bone morphogenetic proteins and Sox9 overexpression on extracellular matrix metabolism of bovine nucleus pulposus cells.
AU Zhang, Yejia [Reprint Author]; An, Howard S.; Thonar, Eugene J. -M. A.; Chubinskaya, Susan; He, Tong-Chuan; Phillips, Frank M.
CS Thomas Jefferson Univ, Dept Rehabil Med, 25 S 9th St, Philadelphia, PA 19107 USA
Yejia_zhang@rush.edu
SO Spine, (SEP 1 2006) Vol. 31, No. 19, pp. 2173-2179.
CODEN: SPINDD. ISSN: 0362-2436.
DT Article
LA English
ED Entered STN: 18 Oct 2006
Last Updated on STN: 18 Oct 2006
AB Study Design. An in vitro biologic study of the effects of adenovirus expressing bone morphogenetic proteins (BMPs) and adenovirus expressing Sox9 on extracellular matrix metabolism by bovine nucleus pulposus cells.Objective. To compare the effects of recombinant adenoviral vectors expressing various BMPs (2, 3, 4, 5, 7, 8, 10, 11, 12, 13, 14, and 15) and Sox9 on extracellular matrix accumulation by bovine nucleus pulposus cells.Summary of Background Data. Nucleus pulposus matrix production may be promoted by transducing the cells with genes that permit the sustained expression of growth factors. The choice of the particular factors or BMPs to be studied for these applications has been largely based on the commercial availability of such products. To our knowledge, this study is the first effort to evaluate systematically the relative effectiveness of the various members of the ***BMP*** family in promoting intervertebral disc matrix repair.Methods. Adult bovine nucleus pulposus cells cultured in monolayer were transduced with adenoviruses expressing human ***BMP*** -2, 3, 4, 5, 7, 8, 10, 11, 12, 13, 14, and 15, and adenovirus expressing Sox9. Proteoglycan and collagen accumulation, and cell proliferation were measured 6 days after viral transduction. As a positive control, cells were cultured without any exogenous gene in the presence of recombinant human (rh) ***BMP*** -7.Results. Nucleus pulposus cells transduced with adenoviruses expressing ***BMP*** -2, 3, 4, 5, 7, 8, 10, 13, 15, and Sox9 accumulated more proteoglycans than nucleus pulposus cells transduced with adenovirus expressing green fluorescent protein (control). It is noteworthy that nucleus pulposus

cells transduced with adenoviruses expressing ***BMP*** -2 and 7 resulted in essentially as great a stimulation of proteoglycan accumulation as nucleus pulposus cells maintained in the presence of rhBMP-7 (adenoviruses expressing ***BMP*** -2: 104% increase; adenoviruses expressing ***BMP*** -7: 162% increase; and rhBMP-7: 120% increase). Nucleus pulposus cells transduced with ***BMP*** -2, 4, 5, 7, 8, 10, 14, 15, and Sox9 accumulated significantly more collagen compared to nucleus pulposus cells transduced with adenovirus expressing green fluorescent protein; adenoviruses expressing ***BMP*** -4 and 14 were the most effective (552% and 661% increase, respectively). Nucleus pulposus cells also proliferated, as measured by deoxyribonucleic acid content, when transduced with adenoviruses expressing ***BMP*** -2 and 8.Conclusions. To our knowledge, for the first time, we have shown the relative effectiveness of 12 different BMPs and Sox9 in stimulating ***proteoglycan*** and collagen ***production*** by nucleus pulposus cells. Adenoviruses expressing ***BMP*** -2 and 7 were the most effective in stimulating proteoglycan accumulation, while adenoviruses expressing ***BMP*** -4 and 14 were the most effective in stimulating collagen accumulation. To our knowledge, this study is the first to compare the relative effectiveness of various BMPs and Sox9 on extracellular matrix accumulation by nucleus pulposus cells, and could help to develop more efficacious approaches to the treatment of degenerating intervertebral discs.

L6 ANSWER 6 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
DUPLICATE 3
AN 2007:154567 BIOSIS <<LOGINID::20071022>>
DN PREV200700154183
TI Bone morphogenetic protein 7 (***bmp*** -7) stimulates ***Proteoglycan*** ***synthesis*** in human osteoarthritic chondrocytes in vitro.
AU Stoeve, J. [Reprint Author]; Schneider-Wald, B.; Scharf, H. -P.; Schwarz, M. L.
CS Univ Heidelberg, Univ Hosp Mannheim, Fac Clin Med, Dept Orthopaed Surg, Theodor Kutzer Ufer 1-3, D-68167 Mannheim, Germany
johannes.stoeve@ortho.ma.uni-heidelberg.de
SO Biomedicine & Pharmacotherapy, (DEC 2006) Vol. 60, No. 10, pp. 639-643.
CODEN: BIPHEX. ISSN: 0753-3322.
DT Article
LA English
ED Entered STN: 7 Mar 2007
Last Updated on STN: 7 Mar 2007
AB ***BMP*** -7 is a member of the TGF-beta superfamily which is supposed to be one of the most potent anabolic factors of chondrocytes. In this study we analysed the effect of ***BMP*** -7 on three dimensional cultured chondrocytes with and without serum. Cartilage samples from fourteen patients with osteoarthritis of the knee were harvested and chondrocytes were cultivated in alginate-beads with and without serum supplementation (10% FCS). ***BMP*** -7 was added in three different concentrations (200, 600 and 1000 ng/ml). After 4 and 21 days PG concentration was determined by a Blyscan-Assay. For gene expression analysis of aggrecan (AGG) quantitative Lightcycler-PCR was used to estimate the mRNA levels. Under serumfree culture conditions there was no stimulation after 4 days but there was a twofold increase of PG concentration after 21 days. Using ***BMP*** -7 together with serum supplemented medium we found comparable results, however not as pronounced. AGG expression was increased only after 4 days but not after 21 days. Beside a stimulatory effect under serumfree conditions we also found a stimulatory effect of ***BMP*** -7 in the presence of serum. This study pronounces that ***BMP*** -7 might be a suitable anabolic activator of osteoarthritic chondrocytes. (c) 2006 Elsevier Masson SAS. All rights reserved.

L6 ANSWER 7 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
DUPLICATE 4
AN 2006:616288 BIOSIS <<LOGINID::20071022>>
DN PREV200600612450
TI Immortalized cell lines from mouse xiphisternum preserve chondrocyte phenotype.
AU Majumdar, Manas K. [Reprint Author]; Chockalingam, Priya S.; Bhat, Ramesh A.; Sheldon, Richard; Keohan, Cristin; Blanchet, Tracey; Glasson, Sonya; Morris, Elisabeth A.
CS Wyeth Res, Dept Womens Hlth and Musculoskeletal Biol, 200 CambridgePk Dr,
Cambridge, MA 02140 USA
mmajumdar@wyeth.com
SO Journal of Cellular Physiology, (NOV 2006) Vol. 209, No. 2, pp. 551-559.
CODEN: JCLLAX. ISSN: 0021-9541.
DT Article
LA English
ED Entered STN: 15 Nov 2006
Last Updated on STN: 15 Nov 2006
AB Chondrocytes are unique to cartilage and the study of these cells in vitro is important for advancing our understanding of the role of these cells in normal homeostasis and disease including osteoarthritis (OA). As there are limitations to the culture of primary chondrocytes, cell lines have been developed to overcome some of these obstacles. In this study, we developed a procedure to immortalize and characterize chondrocyte cell lines from mouse xiphisternum. The cells displayed a polygonal to fibroblastic morphology in monolayer culture. Gene expression studies using quantitative PCR showed that the cell lines responded to bone morphogenetic protein 2 (***BMP*** -2) by increased expression of matrix molecules, aggrecan, and type II collagen together with transcriptional factor, Sox9. Stimulation by IL-1 results in the increased expression of catabolic effectors including MMP-13, nitric oxide synthase, ADAMTS4, and ADAMTS5. Cells cultured in alginate responded to ***BMP*** -2 by increased ***synthesis*** of ***proteoglycan*** (PG), a major matrix molecule of cartilage. IL-1 treatment of cells in alginate results in increased release of PG into the conditioned media. Further analysis of the media showed the presence of Aggrecanase-cleaved aggrecan fragments, a signature of matrix degradation. These results show that the xiphisternum chondrocyte cell lines preserve their chondrocyte phenotype cultured in either monolayer or 3-dimensional alginate bead culture systems. In summary, this study describes the establishment of chondrocyte cell lines from the mouse xiphisternum that may be useful as a surrogate model system to understand chondrocyte biology and to shed light on the underlying mechanism of pathogenesis in OA.

L6 ANSWER 8 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2006495122 EMBASE <<LOGINID::20071022>>
TI Indian and sonic hedgehogs regulate synchondrosis growth plate and cranial base development and function.
AU Young B.; Minugh-Purvis N.; Shimo T.; St-Jacques B.; Iwamoto M.; Enomoto-Iwamoto M.; Koyama E.; Pacifici M.
CS M. Pacifici, Department of Orthopaedic Surgery, Thomas Jefferson University, Philadelphia, PA 19017, United States.
maurizio.pacifici@jefferson.edu
SO Developmental Biology, (1 Nov 2006) Vol. 299, No. 1, pp. 272-282.
Refs: 49
ISSN: 0012-1606 CODEN: DEBIAO
PUI S 0012-1606(06)01033-5
CY United States
DT Journal; Article
FS 001 Anatomy, Anthropology, Embryology and Histology
021 Developmental Biology and Teratology
029 Clinical and Experimental Biochemistry
LA English
SL English
ED Entered STN: 26 Oct 2006
Last Updated on STN: 26 Oct 2006
AB The synchondroses consist of mirror-image growth plates and are critical for cranial base elongation, but relatively little is known about their formation and regulation. Here we show that synchondrosis development is abnormal in Indian hedgehog-null mice. The Ihh(-/-) cranial bases displayed reduced growth and chondrocyte proliferation, but chondrocyte hypertrophy was widespread. Rather than forming a typical narrow zone, Ihh(-/-) hypertrophic chondrocytes occupied an elongated central portion of each growth plate and were flanked by immature collagen II-expressing chondrocytes facing perichondrial tissues. Endochondral ossification was delayed in much of the Ihh(-/-) cranial bases but, surprisingly, was unaffected most posteriorly. Searching for an explanation, we found that notochord remnants near incipient spheno-occipital synchondroses at E13.5 expressed Sonic hedgehog and local chondrocytes expressed Patched, suggesting that Shh had sustained chondrocyte maturation and occipital ossification. Equally unexpected, Ihh(-/-) growth plates stained poorly with Alcian blue and contained low aggrecan transcript levels. A comparable difference was seen in cultured wild-type versus Ihh(-/-) synchondrosis chondrocytes. Treatment with exogenous Ihh did not fully restore normal proteoglycan levels in mutant cultures, but a combination of Ihh and ***BMP*** -2 did. In summary, Ihh is required for multiple processes during synchondrosis and cranial base development, including growth plate zone organization, chondrocyte orientation, and ***proteoglycan*** ***production*** . The cranial base appears to be a skeletal structure in which growth and ossification patterns along its antero-posterior axis are orchestrated by both Ihh and Shh. .COPYRGT. 2006 Elsevier Inc. All rights reserved.

L6 ANSWER 9 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
DUPLICATE 5
AN 2006:202863 BIOSIS <<LOGINID::20071022>>
DN PREV200600194598
TI Stimulatory effects of distinct members of the bone morphogenetic protein family on ligament fibroblasts.
AU Bobacz, K. [Reprint Author]; Ullrich, R.; Amoyo, L.; Erlacher, L.; Smolen, J. S.; Graninger, W. B.
CS Allgemeines Krankenhaus Wien, Dept Internal Med 3, Div Rheumatol, Waehringer Guertel 18-20, A-1090 Vienna, Austria
klaus.bobacz@univie.ac.at
SO Annals of the Rheumatic Diseases, (FEB 2006) Vol. 65, No. 2, pp. 169-177,164.
CODEN: ARDIAO. ISSN: 0003-4967.
DT Article
LA English
ED Entered STN: 22 Mar 2006
Last Updated on STN: 22 Mar 2006
AB Objective: To investigate effects of cartilage derived morphogenetic protein-1 and -2 (CDMP-1, CDMP-2), bone morphogenetic protein (***BMP***)-7 and ***BMP*** -6 on metabolism of ligament fibroblasts and their osteogenic or chondrogenic differentiation potential.Methods: Ligament fibroblasts were obtained from 3 month old calves, plated as monolayers or micromass cultures, and incubated with or without CDMP-1, CDMP-2, ***BMP*** -7, and ***BMP*** -6. Expression of the indicated

growth factors was assessed by RT-PCR and western immunoblotting. The presence of their respective type I and II receptors, and lineage related markers, was investigated in stimulated and unstimulated cells by RT-PCR and northern blotting. Biosynthesis of matrix proteoglycans was assessed by [S-35] sulphate incorporation in monolayers. Alcian blue and toluidine blue staining was done in micromass cultures.Results: CDMP-1, CDMP-2, ***BMP*** -7, and ***BMP*** -6 were detected on mRNA and on the protein level. Type I and II receptors were endogenously expressed in unstimulated ligament fibroblasts. The growth factors significantly stimulated total ***proteoglycan*** ***synthesis*** as assessed by [S-35] sulphate incorporation. Toluidine blue staining showed cartilage-specific metachromasia in the growth factor treated micromass cultures. Transcription analysis of stimulated ligament fibroblasts demonstrated coexpression of chondrocyte markers but no up regulation of osteogenic markers.Conclusion: CDMP-1, CDMP-2, ***BMP*** -7, and ***BMP*** -6 and their receptors were expressed in ligament tissue. These growth factors induced matrix synthesis in fibroblasts derived from bovine ligament. The preferential expression of cartilage markers in vitro suggests that CDMP-1, CDMP-2, ***BMP*** -7, and ***BMP*** -6 have the potential to induce differentiation towards a chondrogenic phenotype in ligament fibroblasts. Thus, fibroblasts from ligaments may serve as a source for chondrogenesis and tissue repair.

L6 ANSWER 10 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2006:1306675 CAPLUS <<LOGINID::20071022>>
DN 146:475813
TI Effects of dexamethasone on proliferation and differentiation of human chondrocytic cells (USAC)
AU Nishiuma, Nobuyuki; Kakuta, Saburo; Yoshizawa, Yasumasa; Yagami, Kimitoshi; Nagumo, Masao
CS Department of Maxillofacial Surgery, Showa University School of Dentistry, 2-1-1 Kitasenzoku, Ohta-ku, Tokyo, 145-8515, Japan
SO Showa Shigakkai Zasshi (2006), 26(2), 133-140
CODEN: SSZADC; ISSN: 0285-922X
PB Showa Daigaku Showa Shigakkai
DT Journal
LA Japanese
AB While glucocorticoids are generally used for patients with articular rheumatism or joint diseases, significant side effects of these agents such as fractures due to osteonecrosis of the femur head or osteoporosis have been also reported. In the field of maxillofacial surgery, osteonecrosis of the temporomandibular condyle has been reported. We have established a cell line (USAC) which expresses chondrocytic and osteoblastic characteristics in vivo and in vitro. In this study, the effects of glucocorticoid (dexamethasone: DEX) on the proliferation and differentiation of USAC were examd. DEX inhibited cell proliferation dose-dependently. At the status just before confluency, the ***synthesis*** of ***proteoglycan*** , collagen type II (Col II) and osteocalcin (OC), which are markers of chondrocytic and osteoblastic differentiation, was immediately enhanced by the addn. of DEX. However, an increase in alk. phosphatase activity, which implies the onset of calcification, was not shown by the addn. of DEX. Interestingly, on days 3 and 7 of cultivation with DEX, expression of mRNA and protein synthesis of Col II and OC had decreased. Though DEX also enhanced the synthesis of Col II and OC in cells pretreated with ***BMP*** , the level of change was more dominant in OC than Col II. These results indicate that DEX not only inhibits cell proliferation, but also modulates cell differentiation.

L6 ANSWER 11 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 6
AN 2006:448520 BIOSIS <<LOGINID::20071022>>
DN PREV200600454285
TI Transgene-activated mesenchymal cells for articular cartilage repair: a comparison of primary bone marrow-, perichondrium/periosteum- and fat-derived cells.
AU Park, Jung; Gelse, Kolja; Frank, Susi; von der Mark, Klaus; Aigner, Thomas; Schneider, Holm [Reprint Author]
CS Univ Erlangen Nurnberg, Dept Expt Med 1, Gluckstr 6, D-91054 Erlangen, Germany
hschneid@molmed.uni-erlangen.de
SO JOURNAL OF GENE MEDICINE, (JAN 2006) Vol. 8, No. 1, pp. 112-125. ISSN: 1099-498X. E-ISSN: 1521-2254.
DT Article
LA English
ED Entered STN: 13 Sep 2006
Last Updated on STN: 13 Sep 2006
AB Background Adult primary mesenchymal cells of different origin which can be obtained with minor donor site morbidity are considered for articular cartilage repair. This study aims at a comparison of their chondrogenic potential.Methods Mesenchymal cells were isolated from perichondrium/periosteum, bone marrow or fat of adult rats and found to be positive for the stem-cell-related antigens Sca-1, c-Kit, CD10, CD13 and CD90 by reverse transcription polymerase chain reaction (RT-PCR). Chondrogenic differentiation was induced by applying recombinant bone morphogenetic protein-2 (***BMP*** -2) or adenoviral vectors carrying ***BMP*** -2 cDNA, followed by micromass culture. The stimulated cells were characterized by RT-PCR, cell proliferation and apoptosis assays. Expression of aggrecan, collagen type I, II, LX and X and alkaline phosphatase genes was analyzed by RT-PCR, immunofluorescence and immunohistochemistry in comparison with unstimulated control cells. Adenovirally stimulated cells were transplanted into mechanically generated partial-thickness cartilage lesions in the patellar groove of the rat femur. Quality and integration of the repair tissues were assessed by histochemical and immunohistochemical methods.Results Stimulation with ***BMP*** -2 or AdBMP-2 led to an up-regulation of cartilage-specific gene expression in all three cell populations studied, most rapidly and prominently in the perichondrial/periosteal cells, which showed a 3200-fold increase of type II collagen mRNA and reached the highest absolute levels of type II and IX collagen transcripts after stimulation. Similar results were obtained for the bone marrow stromal cells (BMSC), while the respective transcript levels in fat stromal cells declined after an initial more than 30-fold elevation. Following transplantation in vivo, AdBMP-2-infected perichondrial/periosteal cells ***produced*** a ***proteoglycan*** -rich, type II collagen-positive matrix with only faint staining for type I collagen. The repair tissue originating from AdBMP-2-infected BMSC showed less intense type II collagen staining, but a relatively proteoglycan-rich matrix, weakly positive for type I collagen. Transgene-activated fat stromal cells formed rather fibrous tissue mainly composed of type I Collagen. Unstimulated cells of the three different populations gave only rise to fibrous tissue.Conclusions Perichondrium/periosteum-derived cells and BMSC seem superior to cells isolated from fat with respect to forming hyaline cartilaginous tissue. A chondrogenic stimulus, e.g. by transfer of ***BMP*** -2 cDNA, appears to be required for initiation and support of chondrogenic differentiation. Copyright (c) 2005 John Wiley & Sons, Ltd.

L6 ANSWER 12 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 7
AN 2006:122925 BIOSIS <<LOGINID::20071022>>
DN PREV200600118073
TI Changes in secreted and cell associated ***proteoglycan*** ***synthesis*** during conversion of myoblasts to osteoblasts in response to bone morphogenetic protein-2: Role of decorin in cell response to ***BMP*** -2.
AU Gutierrez, Jaime; Osses, Nelson; Brandan, Enrique [Reprint Author]
CS Pontificia Univ Catolica Chile, Dept Biol Celular and Mol, Fac Ciencias Biol, Ctr Regulac Celular and Patol,MIFAB, Casilla 114-D, Santiago, Chile
ebrandan@bio.puc.cl
SO Journal of Cellular Physiology, (JAN 2006) Vol. 206, No. 1, pp. 58-67.
CODEN: JCLLAX. ISSN: 0021-9541.
DT Article
LA English
ED Entered STN: 15 Feb 2006
Last Updated on STN: 15 Feb 2006
AB Proteoglycans have been identified within the extracellular matrices (ECM) of bone and are known to play a role in ECM assembly, mineralization, and bone formation. Bone morphogenetic protein-2 (***BMP*** -2) specifically converts the differentiation pathway of C2C12 myoblasts into that of osteoblast lineage cells. Microarray analyses of the mouse myoblast cell line C2C12 and its differentiation into osteoblastic cells in response to ***BMP*** -2 have suggested the up-regulation of several proteoglycan species, although there is a lack of biochemical evidence for this response. In this study we have biochemically analyzed and characterized the proteoglycan populations that are induced in C2C12 cells upon osteoblastic differentiation produced by ***BMP*** -2. An important and specific increase in the synthesis of secreted decorin was observed in ***BMP*** -2-treated cells, as compared to untreated myoblasts and myoblasts induced to differentiate into myotubes. Decorin was seen to contain larger glycosaminoglycan (GAG) chains in induced than in non-induced cells. ***BMP*** -2 also produced an augment in the synthesis of different heparan sulfate proteoglycans such syndecan-2,-3, glypican, and perlecan in detergent-soluble and non-soluble cellular fractions. We also examined whether the evident changes induced by ***BMP*** -2 in secreted decorin could have a functional role. ***BMP*** -2 signaling dependent as well as induction of alkaline phosphatase (ALP) activity was diminished in decorin null myoblasts compared to wild type myoblats although cell surface level of BPM-2 receptors was unchanged. These results are the first biochemical evidence and analysis for the effect of ***BMP*** -2 on the ***synthesis*** of ***proteoglycan*** during osteogenic conversion of myoblasts and suggest a role for decorin in cell response to ***BMP*** -2.

L6 ANSWER 13 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1239076 CAPLUS <<LOGINID::20071022>>
DN 144:641
TI Intracellular delivery of ***osteoinductive*** fusion proteins for inducing bone formation and disc regeneration
IN Titus, Frances; Marx, Jeffrey; Drapeau, Susan; Boden, Scott; Yoon, Sangwook
PA Medtronic Sofamor Danek, USA
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005111058	A1	20051124	WO 2004-US9127	20040413
WO 2005111058	A9	20070118		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1740600 A1 20070110 EP 2004-749433 20040413
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR
JP 2007505621 T 20070315 JP 2006-526862 20040413
CN 1934123 A 20070321 CN 2004-80008027 20040413
IN 2005KN02097 A 20070810 IN 2005-KN2097 20051024
PRAI US 2003-456551P P 20030324
WO 2004-US9127 W 20040413
AB The invention provides a method for intracellular delivery of ***osteoinductive*** proteins fused with transduction domains and uses of the fusion proteins to induce osteogenesis and to promote ***proteoglycan*** ***synthesis*** . An expression construct encoding a cell-permeable polypeptide and an ***osteoinductive*** polypeptide is introducing into suitable host cells such as multipotent progenitor cells to induce bone formation in vivo. The cell-permeable polypeptide may be chosen from the group consisting of HIV-TAT, VP-22, a growth factor signal peptide sequence, Pep-1, etc.
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:1326759 CAPLUS <<LOGINID::20071022>>
DN 144:146854
TI HSPG synthesis by zebrafish Ext2 and extl3 is required for Fgf10 signalling during limb development
AU Norton, William H. J.; Ledin, Johan; Grandel, Heiner; Neumann, Carl J.
CS European Molecular Biology Laboratory (EMBL), Heidelberg, 69117, Germany
SO Development (Cambridge, United Kingdom) (2005), 132(22), 4963-4973
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Heparan sulfate proteoglycans (HSPGs) are known to be crucial for signaling by the secreted Wnt, Hedgehog, ***Bmp*** , and Fgf proteins during invertebrate development. However, relatively little is known about their effect on developmental signaling in vertebrates. Here, we report the anal. of daedalus, a novel zebrafish pectoral fin mutant. Positional cloning identified fgf10 as the gene disrupted in daedalus. We find that fgf10 mutants strongly resemble zebrafish ext2 and extl3 mutants, which encode glycosyltransferases required for heparan sulfate biosynthesis. This suggests that HSPGs are crucial for Fgf10 signaling during limb development. Consistent with this proposal, we observe a strong genetic interaction between fgf10 and extl3 mutants. Furthermore, application of Fgf10 protein can rescue target gene activation in fgf10, but not in ext2 or extl3 mutants. By contrast, application of Fgf4 protein can activate target genes in both ext2 and extl3 mutants, indicating that ext2 and extl3 are differentially required for Fgf10, but not Fgf4, signaling during limb development. This reveals an unexpected specificity of HSPGs in regulating distinct vertebrate Fgfs.
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 8
AN 2006:126304 BIOSIS <<LOGINID::20071022>>
DN PREV200600128171
TI Transduced bovine articular chondrocytes affect the metabolism of cocultured nucleus pulposus cells in vitro: Implications for chondrocyte transplantation into the intervertebral disc.
AU Zhang, Yejia; Li, Zhen; Thonar, Eugene J.-M. A.; An, Howard S.; He, Tong-Chuan; Pietryla, Daniel; Phillips, Frank M. [Reprint Author]
CS Midw Orthopaed, Suite 1063,1725 W Harrison St, Chicago, IL 60612 USA
frank.phillips@rushortho.com
SO Spine, (DEC 1 2005) Vol. 30, No. 23, pp. 2601-2607.
CODEN: SPINDD. ISSN: 0362-2436.
DT Article
LA English
ED Entered STN: 15 Feb 2006
Last Updated on STN: 15 Feb 2006
AB Study Design. Biologic study on the effects of coculture of bovine articular chondrocytes transduced ex vivo with genes expressing bone morphogenetic proteins (BMPs) on nucleus pulposus (NP) cells.Objective. To evaluate the effects of bovine articular chondrocytes transduced with adenoviruses expressing various BMPs on ***proteoglycan*** and collagen ***production*** , and cellular proliferation of NP cells in vitro.Summary of Background Data. Matrix synthesis by intervertebral disc cells is promoted by exposing the cells to growth factors or delivering genes that permit sustained expression of growth factors. We propose a novel therapeutic approach involving delivery of autologous chondrocytes, transduced ex vivo with bioactive proteins, to provide both the cells and proteins required to stimulate disc healing.Methods. Adult bovine articular chondrocytes were transduced with adenoviruses (Ads) expressing either ***BMP*** -2, 4, 5, 7, 10, or 13 and plated as monolayers. Bovine NP cells encapsulated in alginate beads were cocultured, floating in the medium. Proteoglycan and collagen accumulation, and NP cell proliferation were measured after 6 days of coculture. As a positive control, beads were cocultured with articular chondrocytes in the presence of rhBMP-7.Results: NP cells cocultered with articular chondrocytes transduced with BMPs-2, 4, 7, and 10 accumulated significantly ($P = 0.05$) more proteoglycan than when cocultured with chondrocytes transduced with AdGFP (control) [AdBMP-2: 23.6%; AdBMP-4: 27.0%; AdBMP-7: 129.1%; AdBMP-10: 102.1% increases respectively]. Collagen accumulation was significantly ($P < 0.05$) increased by NP cells cocultured with articular chondrocytes transduced with BMPs-2, 4, 5, and 7. [AdBMP-2: 104.6%; AdBMP-4: 40.6%; AdBMP-5: 58.6%; AdBMP-7: 55.5% increases respectively]. NP cells proliferated when cocultured with articular chondrocytes transduced with AdBMP-2 and -7.Conclusions: Bovine NP cells are stimulated to produce proteoglycans and collagen when exposed to chondrocytes transduced with genes for various BMPs. If applied to the treatment of disc degeneration, this strategy could provide the disc with not only metabolically active chondrocytes but also promote matrix replenishment by stimulating native NP cells.

L6 ANSWER 16 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 9
AN 2005:334021 BIOSIS <<LOGINID::20071022>>
DN PREV200510126482
TI Bone morphogenetic protein 9 is a potent anabolic factor for juvenile bovine cartilage, but not adult cartilage.
AU Hills, Robert L. [Reprint Author]; Belanger, Leona M.; Morris, Elisabeth A.
CS Pfizer, BB3K,700 Chesterfield Pkwy, St Louis, MO 63017 USA
robert.l.hills@pfizer.com
SO Journal of Orthopaedic Research, (MAY 2005) Vol. 23, No. 3, pp. 611-617.
CODEN: JOREDR. ISSN: 0736-0266.
DT Article
LA English
ED Entered STN: 31 Aug 2005
Last Updated on STN: 31 Aug 2005
AB Members of the bone morphogenetic protein (***BMP***) group of the TGF-beta superfamily have been shown to enhance matrix synthesis and maintain cartilage phenotype in long-term culture. These proteins have also been shown to augment cartilage repair in vivo, and may be of potential therapeutic benefit in the treatment of damaged articular cartilage. The present study was undertaken to examine the effects of ***BMP*** -9 on the metabolism of juvenile and adult bovine cartilage in vitro, and to compare the effects to those produced by two previously characterized BMPs: ***BMP*** -2 and 13 (CDMP-2). ***BMP*** -9 lead to a 7-8-fold stimulation of ***proteoglycan*** ***synthesis*** at the highest concentration tested, and a 6.4-fold stimulation of collagen synthesis at a concentration of 50 ng/mL in juvenile cartilage. ***BMP*** -2 also lead to a 7-8-fold increase in ***proteoglycan*** ***synthesis*** at the highest concentration tested, and was able to induce collagen synthesis 6.4-fold, but at a concentration of 1000 ng/mL. Proteoglycans isolated from ***BMP*** -9 treated cartilage exhibited an increased hydrodynamic size possibly due to increased glycosaminoglycan substitution or decreased C-terminal proteolysis. Consistent with the idea of limited C-terminal proteolysis, ***BMP*** -9 treatment lead to a significant reduction in the turnover rate of proteoglycans in juvenile explants. Interestingly, all three BMPs were unable to induce a measurable anabolic response in adult cartilage explants. (c) 2005 Orthopaedic Research Society. Published by Elsevier Ltd. All rights reserved.

L6 ANSWER 17 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:845167 CAPLUS <<LOGINID::20071022>>
DN 143:302990
TI Transcriptional regulation of hyaluronan synthases by bone morphogenetic protein-2 in mouse primary chondrocytes
AU Sawai, Takahiro; Itano, Naoki; Kimata, Koji
CS Dep. Orthopaedic Surg., The Jikei Univ. Sch. Med., Japan
SO Aichi Ika Daigaku Igakkai Zasshi (2005), 33(1), 1-6
CODEN: AIDZAC; ISSN: 0301-0902
PB Aichi Ika Daigaku Igakkai
DT Journal
LA Japanese
AB Bone morphogenetic proteins (BMPs) were originally identified in demineralized bone matrix as a protein inducing bone formation in vivo. BMPs form a large family of morphogens for cartilage and play a crit. role in bone morphogenesis. ***BMP*** -2 was first cloned and expressed by Wozney and co-worker. Recombinant ***BMP*** -2, ***BMP*** -4, and ***BMP*** -7 induce cartilage differentiation in vivo and chondrogenesis of chick limb bud mesodermal cells in vitro. ***BMP*** -4 and ***BMP*** -7 can maintain the ***proteoglycan*** ***synthesis*** in chem. defined serum-free medium. The biosynthesis of hyaluronan (HA) is a key step in chrondrogenesis. Hyaluronan synthases (HAS1, 2 and 3) are functionally crit. in biosynthesis of HA. In the present study, we have investigated the potential actions of recombinant human ***BMP*** -2 on HA biosynthesis in mouse primary chondrocytes. The results revealed a reciprocal regulation of HAS1 and HAS2 by ***BMP*** -2. HAS2 was stimulated by ***BMP*** -2 while concurrently there was a down regulation of HAS1. There appear to be no effect of ***BMP*** -2 on HAS3.

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AN 2005539646 EMBASE <<LOGINID::20071022>>
TI Molecular therapy of the intervertebral disc.
AU Yoon S.T.
CS Dr. S.T. Yoon, Emory Spine Center, 59 Executive Park South, Atlanta, GA 30029, United States. tim_yoon@emoryhealthcare.org
SO Spine Journal, (Nov 2005) Vol. 5, No. 6 SUPPL., pp. 280S-286S.
Refs: 45
ISSN: 1529-9430 CODEN: SJPOA6
PUI S 1529-9430(05)00095-1
CY United States
DT Journal; General Review; (Review)
FS 022 Human Genetics
030 Clinical and Experimental Pharmacology
033 Orthopedic Surgery
037 Drug Literature Index
039 Pharmacy
004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
LA English
SL English
ED Entered STN: 15 Dec 2005
Last Updated on STN: 15 Dec 2005
AB Background and context: Currently, no biologic treatment is available for disc degeneration. However, many different molecules of potential therapeutic benefit are being investigated. Purpose: Review and categorize the molecules under investigation for potential therapy in preventing or reversing disc degeneration. Study design: Review article. Methods: Review of published articles on molecules that may be useful in biologic therapy of the intervertebral disc. Results: The list of molecules under investigation for potential benefit in biologic therapy of the intervertebral disc repair continues to grow. These molecules are so diverse that they no longer all fall into the classic terminology of "growth factor." Some of these molecules are not growth factors at all and some are not even cytokines. At least four different classes of molecules may be effective in disc repair. These include anticatabolics (eg, tissue inhibitors of metalloproteinase [TIMPs]), mitogens (eg, insulin-like growth factor-1 [IGF-1], platelet-derived growth factor [PDGF]), chondrogenic morphogens (transforming growth factor .beta. [TGF-.beta.] and bone morphogenetic proteins [BMPs]), and intracellular regulators (***LIM*** mineralization protein-1 [LMP-1] and Sox9). Although some in vitro data are available on all of these molecules, few of these molecules have been tested in vivo with an animal model of disc degeneration. Conclusions: As the current screening experiments are concluded, more definitive in vivo systems involving a more realistic degeneration model will be a necessary step before attempting human studies. .COPYRGT. 2005 Elsevier Inc. All rights reserved.

L6 ANSWER 19 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2005539647 EMBASE <<LOGINID::20071022>>
TI Gene therapy for disc repair.
AU Levicoff E.A.; Gilbertson L.G.; Kang J.D.
CS Dr. J.D. Kang, Department of Orthopaedic Surgery, 3471 5th Avenue, Pittsburgh, PA 15213, United States. kangjd@upmc.edu
SO Spine Journal, (Nov 2005) Vol. 5, No. 6 SUPPL., pp. 287S-296S.
Refs: 51
ISSN: 1529-9430 CODEN: SJPOA6
PUI S 1529-9430(05)00096-3
CY United States
DT Journal; General Review; (Review)
FS 022 Human Genetics
030 Clinical and Experimental Pharmacology
033 Orthopedic Surgery
037 Drug Literature Index
039 Pharmacy
004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
LA English
SL English
ED Entered STN: 15 Dec 2005
Last Updated on STN: 15 Dec 2005
AB Background context: Recent advances in our understanding of the biologic makeup and environment of the intervertebral disc (IVD) have led to increased interest in the development of novel treatments for disc degeneration. Certain genes found to alter rates of matrix synthesis and catabolism within the disc have provided targets for scientists seeking to alter the balance between the two. To this end, gene therapy has emerged as a potential therapeutic option, and recent research efforts have yielded very promising results. Purpose: To update and consolidate information regarding the recent advances in gene therapy and its application to IVD degeneration. Studydesign/setting: Review of recent and ongoing research in the field of gene therapy, particularly regarding its application to the treatment of IVD degeneration. Methods: Literature review. Results: With its unique ability to provide sustained delivery of potentially therapeutic agents, gene therapy has shown much promise with regard to the treatment of IVD degeneration. There have been many exciting developments such as safer and more reliable vector constructs, favorable results using therapeutic transgenes in disc cells both in vitro and in vivo, and improvement in transgene regulation, and investigators continue to explore ways in which gene therapy can become a powerful tool in the future treatment of disc degeneration. Conclusions: With continued perseverance and dedication, many advances have been made in the application of gene therapy to the IVD, and it continues to demonstrate great potential to become a powerful tool in the future treatment of disc degeneration. .COPYRGT. 2005 Elsevier Inc. All rights reserved.

L6 ANSWER 20 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2005107496 EMBASE <<LOGINID::20071022>>
TI Induction of chondro-, osteo- and adipogenesis in embryonic stem cells by bone morphogenetic protein-2: Effect of cofactors on differentiating lineages.
AU Zur Nieden N.I.; Kempka G.; Rancourt D.E.; Ahr H.-J.
CS N.I. Zur Nieden, Molecular and Genetic Toxicology, Bayer HealthCare AG, Wuppertal, Germany. nicole.zur.nieden@gmx.net
SO BMC Developmental Biology, (26 Jan 2005) Vol. 5. arn. 1.
Refs: 36
ISSN: 1471-213X E-ISSN: 1471-213X
CY United Kingdom
DT Journal; Article
FS 021 Developmental Biology and Teratology
029 Clinical and Experimental Biochemistry
LA English
SL English
ED Entered STN: 17 Mar 2005
Last Updated on STN: 5 May 2005
AB Background: Recently, tissue engineering has merged with stem cell technology with interest to develop new sources of transplantable material for injury or disease treatment. Eminently interesting, are bone and joint injuries/disorders because of the low self-regenerating capacity of the matrix secreting cells, particularly chondrocytes. ES cells have the unlimited capacity to self-renew and maintain their pluripotency in culture. Upon induction of various signals they will then differentiate into distinctive cell types such as neurons, cardiomyocytes and osteoblasts. Results: We present here that ***BMP*** -2 can drive ES cells to the cartilage, osteoblast or adipogenic fate depending on supplementary co-factors. TGF.beta.(1), insulin and ascorbic acid were identified as signals that together with ***BMP*** -2 induce a chondrocytic phenotype that is characterized by increased expression of cartilage marker genes in a timely co-ordinated fashion. Expression of collagen type IIB and aggrecan, indicative of a fully mature state, continuously ascend until reaching a peak at day 32 of culture to approximately 80-fold over control values. Sox9 and scleraxis, cartilage specific transcription factors, are highly expressed at very early stages and show decreased expression over the time course of EB differentiation. Some smaller proteoglycans, such as decorin and biglycan, are expressed at earlier stages. Overall, proteoglycan biosynthesis is up-regulated 7-fold in response to the supplements added. ***BMP*** -2 induced chondrocytes undergo hypertrophy and begin to alter their expression profile towards osteoblasts. Supplying mineralization factors such as .beta.-glycerophosphate and vitamin D(3) with the culture medium can facilitate this process. Moreover, gene expression studies show that adipocytes can also differentiate from ***BMP*** -2 treated ES cells. Conclusions: Ultimately, we have found that ES cells can be successfully triggered to differentiate into chondrocyte-like cells, which can further alter their fate to become hypertrophic, and adipocytes. Compared with previous reports using a brief ***BMP*** -2 supplementation early in differentiation, prolonged exposure increased chondrogenic output, while supplementation with insulin and ascorbic acid prevented dedifferentiation. These results provide a foundation for the use of ES cells as a potential therapy in joint injury and disease. .COPYRGT. 2005 zur Nieden et al; licensee BioMed Central Ltd.

L6 ANSWER 21 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 10
AN 2005:99845 BIOSIS <<LOGINID::20071022>>
DN PREV200500097544
TI ISSLS prize winner: LMP-1 upregulates intervertebral disc cell production of proteoglycans and BMPs in vitro and in vivo.
AU Yoon, Sangwook Tim [Reprint Author]; Park, Jin Soo; Kim, Keun S.; Li, Jun; Attallah-Wasif, Emad Samir; Hutton, William C.; Boden, Scott D.
CS Sch MedEmory Spine CtrDept Orthopaed Surg, Emory Univ, 2165 N Decatur Rd,
Decatur, GA, 30033, USA
tim_yoon@emoryhealthcare.org
SO Spine, (December 1 2004) Vol. 29, No. 23, pp. 2603-2611. print.
ISSN: 0362-2436 (ISSN print).
DT Article
LA English
ED Entered STN: 9 Mar 2005
Last Updated on STN: 9 Mar 2005
AB Study Design. Experiments using both in vitro tissue culture and in vivo rabbit methods were used to study the effect of ***Lim*** Mineralization Protein-1 (LMP-1) on intervertebral disc (IVD) cell production of proteoglycans and bone morphogenetic proteins (BMPs). Objectives. To determine the effect of LMP-1 overexpression in IVD cells on the production of proteoglycans and BMPs both in vitro and in vivo and to show that LMP-1 mediates the control of ***proteoglycan*** ***production*** through its action on BMPs. Summary of Background Data. Because BMPs are known to increase ***proteoglycan*** ***synthesis*** and LMP-1 is known to upregulate BMPs in certain cells, it was hypothesized that LMP-1 may increase ***proteoglycan*** ***production*** in IVD cells. Methods. DMMB, real-time polymerase chain reaction, and ELISA methods were used to quantitate proteoglycan, mRNA, and protein levels, respectively. Noggin was used to block the effect of the adenovirus carrying LMP-1 (AdLMP-1) on ***proteoglycan*** ***synthesis*** . In vivo experiments using intradiscal AdLMP-1

injection were performed with New Zealand White rabbits. Three weeks later, the mRNA levels of LMP-1, aggrecan, ***BMP*** -2, and ***BMP*** -7 were measured. Results. In vitro experiments revealed that the sulfated glycosaminoglycan (sGAG) and aggrecan mRNA levels were significantly increased with AdLMP-1 treatment. Similarly, ***BMP*** -2 and ***BMP*** -7 mRNA and protein levels increased significantly, but ***BMP*** -4 and ***BMP*** -6 levels were unchanged. Noggin blocked the upregulation of proteoglycan by AdLMP-1. In vivo discs injected with AdLMP-1 had significantly elevated levels of LMP-1, ***BMP*** -2, and ***BMP*** -7 mRNA. Conclusions. LMP-1 overexpression increases disc cellproduction of proteoglycan, ***BMP*** -2, and ***BMP*** -7. LMP-1mediates the control of ***proteoglycan*** ***production*** through its action on ***BMP*** .

L6 ANSWER 22 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 11
AN 2004:143903 BIOSIS <<LOGINID::20071022>>
DN PREV200400131458
TI BIG-3, a novel WD-40 repeat protein, is expressed in the developing growth plate and accelerates chondrocyte differentiation in vitro.
AU Gori, Francesca [Reprint Author]; Demay, Marie B.
CS Endocrine Unit, Massachusetts General Hospital, 50 Blossom Street, Wellman 501, Boston, MA, 02114, USA
gori@helix.mgh.harvard.edu
SO Endocrinology, (March 2004) Vol. 145, No. 3, pp. 1050-1054. print.
CODEN: ENDOAO. ISSN: 0013-7227.
DT Article
LA English
ED Entered STN: 10 Mar 2004
Last Updated on STN: 10 Mar 2004
AB Among the local signaling pathways that regulate the sequential steps of chondrocyte differentiation is the bone morphogenetic protein (***BMP***) signaling pathway. We have identified a novel gene, named BIG-3 (***BMP*** -2-induced gene 3 kb) that is expressed in a ***BMP*** -regulated fashion in the prechondroblastic cell line MLB13MYC clone 17. BIG-3 is also expressed in proliferating and hypertrophic chondrocytes in the developing growth plate in vivo. We undertook studies to address whether BIG-3 played a functional role in chondrocyte differentiation, using mouse clonal chondrogenic ATDC5 cells. BIG-3 protein levels increased during ITS (insulin, transferrin, sodium selenite)-induced ATDC5 differentiation and in response to ***BMP*** -2 treatment. To determine whether stable expression of BIG-3 could alter the program of chondrocytic differentiation, ATDC5 cells were stably transfected with the full-length coding region of BIG-3 (ATDC5-BIG-3) or with the empty vector (ATDC5-EV). Accelerated matrix ***proteoglycan*** ***synthesis*** was observed in the pooled ATDC5-BIG-3 clones. Alkaline phosphatase and osteopontin mRNA levels were also increased in ATDC5-BIG-3 clones compared with ATDC5-EV clones. Stable expression of BIG-3 also accelerated mineralized matrix formation in both the presence and absence of ITS. These findings, which demonstrate that BIG-3 accelerates chondrocyte differentiation in vitro, combined with the observation that BIG-3 is expressed in the growth plate during embryonic development, suggest that this novel protein is likely to play an in vivo regulatory role in the developing growth plate.

L6 ANSWER 23 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 12
AN 2004:81914 BIOSIS <<LOGINID::20071022>>
DN PREV200400083364
TI Adenovirus mediated ***BMP*** -13 gene transfer induces chondrogenic differentiation of murine mesenchymal progenitor cells.
AU Nochi, Hitoshi; Sung, Jin Hyung; Lou, Jueren; Adkisson, H. Davis; Maloney, William J.; Hruska, Keith A. [Reprint Author]
CS Washington University School of Medicine, 660 S. Euclid Street, Campus Box 8208, Saint Louis, MO, 63110, USA
hruska_k@kids.wustl.edu
SO Journal of Bone and Mineral Research, (January 2004) Vol. 19, No. 1, pp. 111-122. print.
ISSN: 0884-0431 (ISSN print).
DT Article
LA English
ED Entered STN: 4 Feb 2004
Last Updated on STN: 4 Feb 2004
AB Chondrogenic/osteogenic differentiation of a mesenchymal progenitor stimulated by ***BMP*** -13 (CDMP-2) was studied. C3H10T1/2 cells were transduced by an adenoviral construct containing ***BMP*** -13 or ***BMP*** -2. ***BMP*** -13 supported chondrogenesis but not terminal differentiation, whereas ***BMP*** -2 stimulated endochondral ossification. The studies show that ***BMP*** -13 may fail to support terminal chondrocyte differentiation. Introduction: Bone morphogenetic protein (***BMP***)-13 is a member of the transforming growth factor beta (TGF-beta) superfamily of growth factors. Although the biological functions of ***BMP*** -13 remain poorly understood, continued postnatal expression of ***BMP*** -13 in articular cartilage suggests that this protein may function in an autocrine/paracrine fashion to regulate growth and maintenance of articular cartilage. The purpose of this study was to elucidate the role of ***BMP*** -13 in chondrogenic differentiation. Materials and Methods: Replication-deficient adenoviruses carrying human ***BMP*** -13 (Adv-hBMP13), bacterial beta-galactosidase (Adv-betagal), and human ***BMP*** -2 (Adv-hBMP2) were constructed. Murine mesenchymal progenitor cells (C3H10T1/2) were transduced with these vectors, and differentiation to the chondrogenic lineage was assessed by reverse transcriptase-polymerase chain reaction (RT-PCR), biochemical, and histological analyses. Results and Conclusions: Our findings revealed that hBMP-13 transduced cells differentiated into round cells that stained with Alcian blue. Analysis of gene expression in hBMP-13-transduced cells demonstrated presence of cartilage-specific markers, absence of hypertrophic chondrocyte specific markers, and upregulation of proteoglycan biosynthesis. In particular, hBMP-13-transduced cells had significantly less and delayed expression of alkaline phosphatase activity and calcium mineral accumulation than hBMP-2-transduced cells. Except for BMPR-IB/ALK-6, expression of ***BMP*** receptors was identified constitutively in C3H10T1/2 cells and was not affected by the presence of either of the BMPs. In summary, hBMP-13, while stimulating chondrogenesis, failed to support differentiation to hypertrophic chondrocytes and endochondral ossification similar to hBMP-2. Thus, this may prove to be a useful strategy for cell-based regeneration of articular cartilage.

L6 ANSWER 24 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN
AN 2004:285009 BIOSIS <<LOGINID::20071022>>
DN PREV200400283766
TI Pro-inflammatory Cytokines, ***BMP*** -2 and Repair of Cartilage.
AU Sandell, Linda J [Reprint Author]; Fukui, Naoshi
CS Orthopaedic Surgery and Cell Biology, Washington University, 1 Barnes Plaza, Box 8233, St. Louis, MO, 63110, USA
sandelll@msnotes.wustl.edu
SO FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 303.6.
http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB.
ISSN: 0892-6638 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 16 Jun 2004
Last Updated on STN: 16 Jun 2004
AB Cartilage degeneration results from an imbalance between anabolism and catabolism. In the search for anabolic factors in the cartilage degenerative disease, osteoarthritis (OA), we found that ***BMP*** -2 levels are increased . In order to determine the cellular response to ***BMP*** -2, cultured chondrocytes were treated with ***BMP*** -2, and expression of type II procollagen and aggrecan genes, as well as the incorporation of (35S)sulfate were determined. The results showed that ***BMP*** -2 has anabolic actions on normal and OA articular chondrocytes. To investigate the mechanism of ***BMP*** -2 up-regulation cartilage, chondrocytes were treated with relevant growth factors and cytokines known to be present in synovial joints, and the expression of ***BMP*** -2 mRNA was evaluated. TGF-Beta1 or IGF-1 did not alter the level of ***BMP*** -2 expression, however, the proinflammatory cytokines IL-1Beta and TNF-(both strongly induced ***BMP*** -2 mRNA and active protein up to 20 fold. The significance of ***BMP*** -2 in cartilage was evaluated in explant culture before and after TNF-(stimulation and inhibition of ***BMP*** activity. The ***BMP*** -2 antagonist noggin suppressed ***proteoglycan*** ***synthesis*** more than 20%, suggesting significant contribution of ***BMP*** -2 to cartilage anabolism in vivo. Further studies showed that ***BMP*** -2 is stimulated by a post-transcriptional mechanism that is specific to differentiated chondrocytes and not seen in progenitor cells. This study demonstrates that the proinflammatory cytokines can induce both catabolism and anabolism in mature chondrocytes. These processes are characteristic of remodeling and potential repair of the extracellular matrix. This mechanism may be of critical importance in the response of chondrocytes to injury. .

L6 ANSWER 25 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:397004 CAPLUS <<LOGINID::20071022>>
DN 138:397329
TI cDNAs encoding rat and human ***LIM*** mineralization proteins and their use in treatment of disk degeneration and disk injury
IN McKay, William F.; Boden, Scott D.; Yoon, Sangwook T.
PA Medtronic Sofamor Danek, USA
SO PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003042368	A2	20030522	WO 2002-US36465	20021114
WO 2003042368	A3	20031016		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,

CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003180266 A1 20030925 US 2002-292951 20021113
CA 2466769 A1 20030522 CA 2002-2466769 20021114
AU 2002343697 A1 20030526 AU 2002-343697 20021114
EP 1465489 A2 20041013 EP 2002-780657 20021114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
CN 1665391 A 20050907 CN 2002-827099 20021114
JP 2005526488 T 20050908 JP 2003-544188 20021114
ZA 2004003714 A 20060222 ZA 2004-3714 20040514
IN 2004KN00763 A 20050916 IN 2004-KN763 20040614
PRAI US 2001-331321P P 20011114
US 2002-292951 A 20021113
US 1988-124238 A 19880729
US 2000-959578 A 20000428
WO 2002-US36465 W 20021114

AB Methods of expressing ***LIM*** mineralization protein in non-osseous mammalian cells, such as stem cells or intervertebral disk cells (e.g., cells of the annulus fibrosus, or cells of the nucleus pulposus) are described. The methods involve transfecting the cells with an isolated nucleic acid comprising a nucleotide sequence encoding a ***LIM*** mineralization protein operably linked to a promoter. Transfection may be accomplished ex vivo or in vivo by direct injection of virus or naked DNA, or by a nonviral vector such as a plasmid. Expression of the ***LIM*** mineralization protein can stimulate proteoglycan and/or collagen prodn. in cells capable of ***producing*** ***proteoglycan*** and/or collagen. Methods for treating disk disease assocd. with trauma or disk degeneration are also described.

L6 ANSWER 26 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 13

AN 2004:88879 BIOSIS <<LOGINID::20071022>>
DN PREV200400091192
TI Bone morphogenetic protein-2 facilitates expression of chondrogenic, not osteogenic, phenotype of human intervertebral disc cells.
AU Kim, Dong-Jun; Moon, Seong-Hwan [Reprint Author]; Kim, Hyang; Kwon, Un-Hye; Park, Moon-Soo; Han, Keong-Jin; Hahn, Soo-Bong; Lee, Hwan-Mo
CS Department of Orthopaedic Surgery, College of Medicine, Yonsei University, No. 134, Shinchondong, Seodaemunku, Seoul, South Korea
shmoon@yumc.yonsei.ac.kr
SO Spine, (December 15 2003) Vol. 28, No. 24, pp. 2679-2684. print.
ISSN: 0362-2436 (ISSN print).
DT Article
LA English
ED Entered STN: 11 Feb 2004
Last Updated on STN: 11 Feb 2004

AB Study Design: In vitro experiment using bone morphogenetic protein-2 (***BMP*** -2) and human intervertebral disc (IVD) cells. Objectives: To demonstrate the effect of ***BMP*** -2 on mRNAs expression (collagen type I, collagen type II, aggrecan, and osteocalcin), ***proteoglycan*** ***synthesis*** , expression of alkaline phosphatase, bone nodule formation in human IVD cells. Summary of Background Data: ***BMP*** -2 was widely known as a powerful agent for ***osteoinduction*** and a crucial growth factor for early chondrogenesis and maintenance of cartilaginous phenotype. ***BMP*** -2 proved to be effective in stimulating ***proteoglycan*** ***synthesis*** in articular chondrocytes and IVD cells. Nevertheless, the effect of ***BMP*** -2 on IVD cells, whether chondrogenic or osteogenic, was not thoroughly elucidated in transcriptional level and histochemical stains. Materials and Methods: Human IVDs were harvested and enzymatically digested. Then IVD cells were cultured three-dimensionally in alginate beads. Osteoblasts were cultured from cancellous bone of ilium for histochemical stains. Recombinant human ***BMP*** -2 (rhBMP-2) was produced by Chinese hamster ovary cells after transduction of ***BMP*** -2 cDNA, then concentrated and purified. Then IVD cell cultures were exposed to various concentrations of rhBMP-2. Reverse transcription-polymerase chain reaction for mRNA expression of aggrecan, collagen type 1, collagen type II, and osteocalcin was performed. Newly ***synthesized*** ***proteoglycan*** was measured by 35S-sulfate incorporation on Sephadex G-25 M in PD 10 columns. As a histochemical examination, alkaline phosphatase and Alizarin red-S stains were used to detect osteogenic marker and bone nodule formation, respectively. Results: In the rhBMP-2 treated cultures, there was increased newly ***synthesized*** ***proteoglycan*** (67% in 300 ng/mL and 200% in 1,500 ng/mL of rhBMP-2) and upregulated expression of aggrecan, collagen type I, and collagen type II mRNA over untreated control. However, rhBMP-2 did not up-regulate expression of osteocalcin mRNA in the given dose and culture period. IVD cell cultures with rhBMP-2 showed no evidence of bone formation in histochemical stains, i.e., alkaline phosphatase and Alizarin red-S, while osteoblast culture exhibited strong positive stains. Conclusions: The rhBMP-2 clearly up-regulated mRNA expression of chondrogenic components and also stimulated ***proteoglycan*** ***synthesis*** without expression of osteogenic phenotype. Taken together, this study raise the possibility of rhBMP-2 can be anabolic agent for regenerating matrix of intervertebral disc.

L6 ANSWER 27 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 14

AN 2003:821043 CAPLUS <<LOGINID::20071022>>
DN 140:105745
TI Expression of bone morphogenetic protein 6 in healthy and osteoarthritic human articular chondrocytes and stimulation of matrix synthesis in vitro
AU Bobacz, K.; Gruber, R.; Soleiman, A.; Erlacher, L.; Smolen, J. S.; Graninger, W. B.
CS University of Vienna, Vienna, Austria
SO Arthritis & Rheumatism (2003), 48(9), 2501-2508
CODEN: ARHEAW; ISSN: 0004-3591
PB John Wiley & Sons, Inc.
DT Journal
LA English

AB To elucidate the role of bone morphogenetic protein 6 (***BMP*** -6) in human articular cartilage, the authors investigated whether ***BMP*** -6 is expressed in adult human articular chondrocytes and analyzed the potential stimulatory effects of ***BMP*** -6 on these cells. In addn., the authors investigated whether osteoarthritic (OA) and normal cartilage chondrocytes behave differently. Endogenous expression of the ***BMP*** -6 gene was examd. by reverse transcription-polymerase chain reaction. ***BMP*** -6 protein was detected by Western immunoblotting. Chondrocytes were grown as monolayer cultures for 7 days in a chem. defined serum-free medium, in the absence or presence of recombinant ***BMP*** -6. ***Proteoglycan*** (PG) ***synthesis*** was measured by 35S-sulfate incorporation into newly synthesized macromols. Cell proliferation was assessed by 3H-thymidine incorporation. ***BMP*** -6 was expressed in both healthy and OA chondrocytes at the mRNA and protein levels. Total PG synthesis was significantly increased after ***BMP*** -6 stimulation of healthy (191%) and OA (150%) chondrocyte cultures. A direct comparison between healthy and OA samples revealed no significant difference. The proliferation rates of normal and OA chondrocytes were not affected by ***BMP*** -6 treatment. Thus, ***BMP*** -6 is endogenously expressed in chondrocytes obtained from OA and normal adult human articular cartilage. Furthermore, ***BMP*** -6 has the potential to stimulate total PG synthesis in human articular chondrocytes derived from normal as well as OA joints. The authors conclude that the presence of ***BMP*** -6 in adult human articular cartilage indicates a functional role for this growth factor in the maintenance of joint integrity.

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 28 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 15

AN 2003:548513 BIOSIS <<LOGINID::20071022>>
DN PREV200300549761
TI Gene transfer of the catabolic inhibitor TIMP-1 increases measured proteoglycans in cells from degenerated human intervertebral discs.
AU Wallach, Corey J.; Sobajima, Satoshi; Watanabe, Yasuhiko; Kim, Joseph S.; Georgescu, Helga I.; Robbins, Paul; Gilbertson, Lars G.; Kang, James D. [Reprint Author]
CS Ferguson Laboratory for Orthopaedic Research, Department of Orthopaedic Surgery, University of Pittsburgh Medical Center, 200 Lothrop Street, PUH C-313, Pittsburgh, PA, 15213, USA
kangjd@msx.upmc.edu
SO Spine, (October 15 2003) Vol. 28, No. 20, pp. 2331-2337. print.
ISSN: 0362-2436 (ISSN print).
DT Article
LA English
ED Entered STN: 19 Nov 2003
Last Updated on STN: 19 Nov 2003

AB Study Design. Cells from degenerated intervertebral discs were transduced with an adenoviral vector delivering cDNA of the catabolic inhibitor, TIMP-1, and alterations in the measured proteoglycan were assessed. Objectives. To assess the potential of TIMP-1 to favorably modify the proteoglycan content of degenerated intervertebral disc cells. Summary of Background Data. Gene therapy with anabolic factors has resulted in increased ***proteoglycan*** ***synthesis*** in intervertebral disc cells. Biochemical analysis of degenerated discs has revealed elevated levels of the catabolic enzymes, matrix metalloproteinase, suggesting an intimate role of these factors in the degenerative process. The use of TIMP-1, an endogenous inhibitor of matrix metalloproteinase, via gene therapy may provide an additional method to alter the degenerative processes occurring in the intervertebral disc. Materials and Methods. Degenerated intervertebral disc were isolated from eight patients, undergoing elective surgical procedures. Cells were cultured in monolayer and transduced with different concentrations of either an adenoviral-tissue inhibitor of metalloproteinase-1 (Ad-TIMP-1) or adenoviral-bone morphogenic protein-2 (Ad- ***BMP*** -2) construct. Cells were cultured in a three-dimensional pellet and ***proteoglycan*** ***synthesis*** was assessed via 35S-sulfur incorporation. Results. Gene delivery of TIMP-1 and ***BMP*** -2 increased measured ***proteoglycan*** ***synthesis*** at each concentration assessed. IVD cells treated with Ad-TIMP-1 demonstrated an optimal response at a multiplicity of infection (MOI) of 100. Cells treated with Ad- ***BMP*** -2 demonstrated a progressive increase in ***proteoglycan*** ***synthesis*** with increasing viral concentrations. Conclusions. Successful delivery of the anticatabolic gene, TIMP-1, results in increased measured proteoglycan in cultured degenerated disc cells. This finding supports catabolic inhibition as a promising avenue of research for the treatment of degenerative disc disease via gene therapy.

L6 ANSWER 29 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 16

AN 2003:933808 CAPLUS <<LOGINID::20071022>>
DN 141:99611

TI Statin stimulates bone morphogenetic protein-2, aggrecan, and type 2 collagen gene expression and ***proteoglycan*** ***synthesis*** in rat chondrocytes
AU Hatano, Hiroshi; Maruo, Akihiro; Bolander, Mark E.; Sarkar, Gobinda
CS MSB 3-69, Department of Orthopedic Research, Mayo Clinic and Foundation, Rochester, MN, 55905, USA
SO Journal of Orthopaedic Science (2003), 8(6), 842-848
CODEN: JOSCFS; ISSN: 0949-2658
PB Springer-Verlag Tokyo
DT Journal
LA English
AB Statins increase bone morphogenetic protein-2 (***BMP*** -2) mRNA expression and subsequently increase new bone formation in vitro. However, the action of statins on the ***BMP*** -2 mRNA regulation of cartilage matrix synthesis by chondrocytes is unknown. We evaluated regulation of ***BMP*** -2, aggrecan, and type II collagen (COL2) mRNA and 35S-labeled ***proteoglycan*** (PG) ***synthesis*** by mevastatin using cultured chondrocytes obtained from articular cartilage of fetal rats. Expression of ***BMP*** -2, aggrecan, and COL2 mRNAs were increased in the presence of 2 .mu.M mevastatin on day 2. However, longer (10 day) culture in the presence of the drug decreased the expression of these mRNAs. PG synthesis was increased 3 days after treating the cells with mevastatin, which was also decreased with longer (10 day) mevastatin treatment. These results suggest that mevastatin increases mRNA expression of ***BMP*** -2, aggrecan, and COL2 as well as PG synthesis by fetal rat chondrocytes early in the treatment period. We suggest that statins have implications for fracture and cartilage repair.
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 30 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 17
AN 2003:933806 CAPLUS <<LOGINID::20071022>>
DN 140:247525
TI ***BMP*** -2 and CDMP-2: stimulation of chondrocyte ***production*** of ***proteoglycan***
AU Li, Jun; Kim, Keun Su; Park, Jin Soo; Elmer, William A.; Hutton, William C.; Yoon, S. Tim
CS Department of Orthopedics, Atlanta VA Medical Center, Emory University, Decatur, GA, 30037, USA
SO Journal of Orthopaedic Science (2003), 8(6), 829-835
CODEN: JOSCFS; ISSN: 0949-2658
PB Springer-Verlag Tokyo
DT Journal
LA English
AB A hallmark of intervertebral disk degeneration is loss of proteoglycans. Cytokines may be used to stimulate proteoglycan prodn. in the disk to reverse or prevent disk degeneration. The effects of bone morphogenetic protein 2 (***BMP*** -2) and cartilage-derived morphogenetic protein 2 (CDMP-2) (singly and jointly) on ***proteoglycan*** ***synthesis*** by a chondrocytic cell line (MC615) were studied. MC615 cells were dosed with ***BMP*** -2, CDMP-2, or both, cultured for 6 days, and then assayed as follows: (1) The proteoglycan content of the medium and extracellular matrix were detd. by dimethyl-methylene blue staining; (2) cell nos. were detd. after 6 days of culture using the Hoechst dye DNA assay; (3) aggrecan mRNA was measured with the reverse transcription-polymerase chain reaction and Northern blotting assays. Both ***BMP*** -2 and CDMP-2 significantly enhanced proteoglycan prodn. and aggrecan mRNA expression in a dose-dependent manner, although ***BMP*** -2 is more effective than CDMP-2 in increasing sulfated proteoglycan prodn. But ***BMP*** -2 and CDMP-2 have only a slight, nonsignificant effect on cell proliferation. There is no evidence of antagonism or synergy between the two growth factors in the aggrecan gene expression.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 31 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 18
AN 2004:11890 CAPLUS <<LOGINID::20071022>>
DN 141:17508
TI Effect of nitric oxide synthase inhibitor on proteoglycan metabolism in repaired articular cartilage in rabbits
AU Sun, Wei; Jin, Da-di; Wang, Ji-xing; Qin, Li-yun; Liu, Xiao-xia
CS Department of Traumatic Surgery, Shenzhen Second People's Hospital, Shenzhen, 518025, Peop. Rep. China
SO Chinese Journal of Traumatology (English Edition) (2003), 6(6), 336-340
CODEN: CJTRFY; ISSN: 1008-1275
PB Chinese Journal of Traumatology (English Edition)
DT Journal
LA English
AB Objective: To study the effect of nitric oxide synthase inhibitor, S-Me thiocarbamate (SMT), on proteoglycan metab. in repaired articular cartilage in rabbits. Methods: Twenty-four male New Zealand white rabbits, aged 8 mo and weighing 2.5 kg .+-. 0.2 kg, were used in this study. Cartilage defects in full thickness were created on the intercondylar articular surface of bilateral femurs of all the rabbits. Then the rabbits were randomly divided into 3 groups (n = 8 in each group). The defects in one group were filled with fibrin glue impregnated with recombinant human bone morphogenetic protein-2 (rhBMP-2, ***BMP*** group), in one group with fibrin glue impregnated with rhBMP-2 and hypodermic injection with SMT (SMT group) and in the other group with nothing (control group). All the animals were killed at one year postoperatively. The tissue sections were stained with safranine O-fast green and analyzed by Quantiment 500 system to det. the content of glycosaminoglycan through measuring the percentage of safranine O-stained area, the thickness of cartilages and the mean gray scale (av. stain intensity). Radiolabeled sodium sulfate (Na235SO4) was used to assess the ***proteoglycan*** ***synthesis*** . Results: At one year postoperatively, the percentage of safranine O-stained area, the mean gray scale and the cartilage thickness of the repaired tissues in SMT group were significantly higher than those of ***BMP*** group ($P < 0.01$) and the control group ($P < 0.05$). Result of incorporation of Na235SO4 showed that the ***proteoglycan*** ***synthesis*** in SMT group was higher than those of ***BMP*** group and the control group ($P < 0.01$). Conclusions: SMT, a nitric oxide synthase inhibitor, can significantly increase the content of glycosaminoglycan and ***proteoglycan*** ***synthesis*** , and computer-based image anal. is a reliable method for evaluating proteoglycan metab.
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 32 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 19
AN 2003:564407 BIOSIS <<LOGINID::20071022>>
DN PREV200300566096
TI Inhibition of proteoglycan and type II collagen synthesis of disc nucleus cells by nicotine.
AU Kim, Keun Su; Yoon, S. Tim [Reprint Author]; Park, Jin Soo; Li, Jun; Park, Moon Soo; Hutton, William C.
CS Emory Spine Center, 2165 North Decatur Road, Decatur, GA, 30033, USA tim_yoon@emoryhealthcare.org
SO Journal of Neurosurgery, (October 2003) Vol. 99, No. 3 Supplement, pp. 291-297. print.
CODEN: JONSAC. ISSN: 0022-3085.
DT Article
LA English
ED Entered STN: 3 Dec 2003
Last Updated on STN: 3 Dec 2003
AB Object: Systemic nicotine has been hypothesized to cause degeneration of the intervertebral disc which in turn decreases vascular supply to the disc through a cholinergic receptor-mediated process. Another possible mechanism may be through direct regulatory effects on disc cells. In this study, the authors tested the hypothesis that nicotine adversely affects nucleus pulposus cells by directly inhibiting ***proteoglycan*** ***synthesis*** and gene expression of type II collagen (Phase I study). They also assessed the hypothesis that nicotine inhibits the bone morphogenetic protein (***BMP***)-2-induced upregulation of extracellular matrix (Phase II study). Methods: Cells were isolated from nucleus pulposus obtained in rat lumbar discs and cultured on a monolayer. Media were treated with nicotine and/or recombinant human (rh) ***BMP*** -2 for 7 days. Sulfated glycosaminoglycan (SO4-GAG) in media was quantified using 1,9-dimethylmethylene blue (DMMB) assay. Gene assay of types I and II collagen, Sox9, and glyceraldehyde-3-phosphate dehydrogenase were quantified using reverse transcriptase-polymerase chain reaction (RT-PCR) and real time PCR. In the Phase I study, nicotine-treated (100 mug/ml) and non-treated cells were compared. The s-GAG production and messenger RNA (mRNA) of type II collagen and Sox9 decreased significantly in the nicotine-treated group. In the Phase II study, five groups were compared: 1) non-treatment; 2) rhBMP-2 only (100 ng/ml); and 3-5) with rhBMP-2 (100 ng/ml) and increasing doses of nicotine (1 (third group), 10, (fourth group), 100 (fifth group) mug/ml). The SO4-GAG production and mRNA of type II collagen and Sox9 decreased significantly in the groups treated with rhBMP-2 combined with 10 and 100 mug/ml of nicotine compared with the group treated with rhBMP-2. Conclusions: The results of this study raise the possibility that nicotine may contribute to the process of disc degeneration by a direct effect on the nucleus pulposus cells, possibly by antagonizing the effect of ***BMP*** -2.

L6 ANSWER 33 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2003080830 EMBASE <<LOGINID::20071022>>
TI AG-041R stimulates cartilage matrix synthesis without promoting terminal differentiation in rat articular chondrocytes.
AU Okazaki M.; Higuchi Y.; Kitamura H.
CS M. Okazaki, Fuji Gotemba Research Laboratory, Chugai Pharmaceutical Co. Ltd., 1-135 Komakado, Gotemba, Shizuoka 412-8513, Japan. okazakimkt@chugai-pharm.co.jp
SO Osteoarthritis and Cartilage, (1 Feb 2003) Vol. 11, No. 2, pp. 122-132.
Refs: 50
ISSN: 1063-4584 CODEN: OSCAEO
CY United Kingdom
DT Journal; Article
FS 030 Clinical and Experimental Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LA English
SL English
ED Entered STN: 6 Mar 2003
Last Updated on STN: 6 Mar 2003

AB Objective: AG-041R, a novel indolin-2-one derivative, has recently been demonstrated to induce systemic hyaline cartilage hyperplasia in rats. The aim of this study was to characterize its anabolic actions on chondrocytes. Design: Chondrocytes were isolated from knee joints of 5-week-old SD rats. Effects of AG-041R on cartilage matrix synthesis were examined by measuring [(35)S]sulfate incorporation into proteoglycans, Alcian blue staining, and Northern blotting of cartilage matrix genes. ALP activity, mineral deposition and the expression of markers for hypertrophic chondrocytes, were assessed for terminal differentiation of chondrocytes. Roles of endogenous TGF-.beta./BMPs and MEK1/Erk signaling in the action of AG-041R were investigated using the neutralizing soluble receptors and the MEK1 inhibitor. Results: AG-041R accelerated ***proteoglycan*** ***synthesis*** assessed by both [(35)S]sulfate incorporation and Alcian blue stainable extracellular matrix accumulation. It also up-regulated the gene expression of type II collagen and aggrecan, as well as tenascin, a marker for articular cartilage. In contrast, AG-041R suppressed ALP activity, mineralization, and the gene expression of type X collagen and Cbfa1, indicating that AG-041R prevents chondrocyte terminal differentiation. AG-041R increased in ***BMP*** -2 mRNA, and the neutralizing soluble receptor for BMPs reversed the stimulatory effects of AG-041R on cartilage matrix synthesis. Moreover, AG-041R activated MEK1/Erk pathway, which was revealed to prevent chondrocyte terminal differentiation. Conclusion: AG-041R stimulates cartilage matrix synthesis without promoting terminal differentiation in rat articular chondrocytes, which is mediated at least in part by endogenous BMPs and Erk. The data demonstrates that AG-041R has a potential to be a useful therapeutic agent for articular cartilage disorders. .COPYRGT. 2002 OsteoArthritis Research Society International. Published by Elsevier Science Ltd. All rights reserved.

L6 ANSWER 34 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2004:13760 BIOSIS <<LOGINID::20071022>>
DN PREV200400017746
TI The hedgehog signaling network.
AU Cohen, M. Michael Jr. [Reprint Author]
CS Dalhousie University, 5981 University Ave., Halifax, NS, B3H 3J5, Canada r.maclean@dal.ca
SO American Journal of Medical Genetics, (November 15 2003) Vol. 123A, No. 1, pp. 5-28. print.
ISSN: 0148-7299 (ISSN print).
DT Article
LA English
ED Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003
AB In the hedgehog signaling network, mutations result in various phenotypes, including, among others, holoprosencephaly, nevoid basal cell carcinoma syndrome, Pallister-Hall syndrome, Greig cephalopolysyndactyly, Rubinstein-Taybi syndrome, isolated basal cell carcinoma, and medulloblastoma. Active Hedgehog ligand is double lipid modified with a C-terminal cholesterol moiety and an N-terminal palmitate. Transport active Hedgehog from the signaling cell to the responding cell occurs through three mechanisms: 1). formation of multimeric Hedgehog which makes it soluble; 2). function of Dispatched in releasing the lipid-anchored protein from the signaling cell; and 3). movement across the plasma membrane of the responding cell by Tout-velu-dependent ***synthesis*** of heparan sulfate ***proteoglycan*** . In the responding cell, active Hedgehogbinds to its receptor Patched, a 12-pass transmembrane protein, which frees Smoothened, an adjacent 7-pass transmembrane protein, for downstream signaling. Patched and Smoothened may shuttle oppositely between the plasma membrane and endocytic vesicles in response to active Hedgehogligand. In downstream signaling, Cubitus interruptus (Gli proteins in vertebrates), Costal 2, Fused, and Suppressor of Fused form a tetrameric complex. Cubitus interruptus is a bifunctional transcription regulator. In the absence of active Hedgehog ligand, a truncated transcriptional repressor is generated that binds target genes and blocks their transcription. In the presence of active Hedgehog ligand, a full length transcriptional activator binds target genes and upregulates their transcription. Target genes include Wingless (Wnt gene family in vertebrates), Decapentaplegic (Bone Morphogenetic Proteins in vertebrates), and Patched. The upregulation of Patched expression, resulting in Patched protein at the cell membrane, sequesters Hedgehog and limits its spread beyond the cells in which it is produced. Thus, a balance is created by the antagonism of Hedgehog and Patched, whose relative concentrations alternate with respect to each other. Many more factors that are essential for the hedgehog signaling network are also discussed: Megalin, Rab23, Hip, GAS1, PKA, GSK3, CK1, Slimb, SAP18, and CBP.

L6 ANSWER 35 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 20
AN 2002:441178 BIOSIS <<LOGINID::20071022>>
DN PREV200200441178
TI Effect of porcine fetal enamel matrix derivative on chondrocyte proliferation, differentiation, and local factor production is dependent on cell maturation state.
AU Dean, D. D.; Lohmann, C. H.; Sylvia, V. L.; Cochran, D. L.; Liu, Y.; Boyan, B. D. [Reprint author]; Schwartz, Z.
CS Department of Orthopaedics, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, MSC 7774, San Antonio, TX, 78229-3900, USA
BoyanB@uthscsa.edu
SO Cells Tissues Organs, (2002) Vol. 171, No. 2-3, pp. 117-127. print.
ISSN: 1422-6405.
DT Article
LA English
ED Entered STN: 14 Aug 2002
Last Updated on STN: 14 Aug 2002
AB Recent studies have shown that porcine fetal enamel matrix derivative (EMD) can enhance the ***osteoinductive*** ability of demineralized freeze-dried bone allograft (DFDBA) in a nude mouse muscle implantation model. This suggests that one or more components of EMD can regulate the process of endochondral ossification initiated by DFDBA. To substantiate this hypothesis, in the current study, chondrocytes in the endochondral pathway at two stages of maturation were tested for their response to EMD. Chondrocytes were isolated from the resting zone and growth zone (prehypertrophic and upper hypertrophic cell zones) of the costochondral growth plate cartilage of adolescent rats. The results showed that the relatively immature resting zone cells responded to EMD with an increase in proliferation and a decrease in differentiation as measured by alkaline-phosphatase-specific activity. In addition, EMD stimulated a fivefold increase in PGE2 production, but was without effect on collagen ***synthesis*** , ***proteoglycan*** sulfation, and TGF-beta1 production. The more mature growth zone cells also responded to EMD with increased proliferation, but alkaline-phosphatase-specific activity was unchanged, and there was only a modest increase in PGE2 production. In contrast to resting zone cells, growth zone cells exhibited a decrease in collagen ***synthesis*** , ***proteoglycan*** sulfation, and TGF-beta1 production. These observations indicate that EMD has prominent effects on cells in the endochondral pathway. In particular, EMD stimulates the production of more cells, but inhibits their maturation. This would increase the pool of cells available for subsequent differentiation in response to other factors.

L6 ANSWER 36 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:215665 CAPLUS <<LOGINID::20071022>>
DN 137:273124
TI Long-term effect of nitric oxide synthase inhibitor on repair of articular cartilage defects
AU Sun, Wei; Wang, Jixing; Jin, Dadi; Liu, Xiaoxia
CS Department of Orthopaedics Surgery, Nanfang Hospital Affiliated to First Military Medical University, Canton, 510515, Peop. Rep. China
SO Zhonghua Yixue Zazhi (Beijing, China) (2002), 82(1), 23-26
CODEN: CHHTAT; ISSN: 0376-2491
PB Zhonghua Yixue Zazhishe
DT Journal
LA Chinese
AB The long-term effect of inducible nitric oxide synthase inhibitor S-methylisothiourea (SMT) on repair of articular cartilage defects was studied. Twenty-four adult New Zealand White rabbits with full-thickness defects of cartilage created in the trochlear groove of their bilateral femurs were divided into three groups randomly, 8 in each group: (1) control group in which nothing was filled into the defects; (2) ***BMP*** group in which the defects were filled with collagen fibrin gel impregnated with recombinant human bone morphogenetic protein (rhBMP); and (3) SMT group in which the defects were filled with collagen fibrin gel impregnated with rhBMP and hypodermic injection of SMT (5 mg kg-1 12 h-1) was given. The animals were killed one year later. The gross appearance of the defects was assessed. The amt. of released NO and the activity of NOS were examd. by chem. colorimetry. The distribution of collagen was examd. by immunohistochem. The ***proteoglycan*** ***synthesis*** and cell activity were assessed by incorporation of radiolabeled sodium sulfate Na352SO4 and bromodeoxyuridine. One year after the defects in SMT group showed greater improvement in margin integration, cellular morphol., and architecture within defect than those in ***BMP*** group and control group (P<0.01). Immunohistochem. showed that there was less type-I collagen and more type-II collagen in SMT group than in the other two groups. Radiolabeled sodium sulfate (Na352SO4) incorporation test showed that the ***proteoglycan*** ***synthesis*** in defects was higher in SMT group than in the other two groups (P<0.01). BrdU incorporation test showed cells in repaired tissue with remarkable proliferation activity. Thus, iNOS inhibitor SMT significantly improves the quality of repair of defective cartilage and delays its degrdn.

L6 ANSWER 37 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 21
AN 2002:192224 BIOSIS <<LOGINID::20071022>>
DN PREV200200192224
TI Radiation-induced reduction of ***BMP*** -induced ***proteoglycan*** ***synthesis*** in an embryonal mesenchymal tissue equivalent using the chicken "limb bud" test.
AU Koelbl, Oliver [Reprint author]; Knaus, Petra; Pohl, Fabian; Flentje, Michael; Sebald, Walter
CS Department of Radiation Therapy, University, Josef-Schneider-Strasse 11, 97080, Wuerzburg, Germany
koelbl@strahlentherapie.uni-wuerzburg.de
SO Strahlentherapie und Onkologie, (August, 2001) Vol. 177, No. 8, pp. 432-436. print.
CODEN: STONE4. ISSN: 0179-7158.
DT Article
LA English
ED Entered STN: 13 Mar 2002

Last Updated on STN: 13 Mar 2002
AB Purpose: Heterotopic ossification (HO) is a common complication following total hip replacement. Clinical studies showed the effectiveness of irradiation for prevention of heterotopic ossification. The mechanism of radiotherapy responsible for the reduction of heterotopic ossification is unclear. The purpose of this study was to find a suitable cell system, which can reproduce in-vitro data resulting from clinical in-vivo studies. The establishment of such a cell model allows detailed analyses of the mechanism of radiotherapy. Method: The chicken limb bud test was used as an in-vitro model. The cells acquired by the limb bud test were irradiated with different doses (0 Gy, 3 Gy, 7 Gy, 10 Gy, 20 Gy). Irradiation was set either 1 hour before, or 1 or 3 days after ***BMP*** -2 incubation. The synthesis of proteoglycans (PGS) upon treatment with bone morphogenetic protein (***BMP***)-2 was measured in cells incubated with ***BMP*** -2 for 4 days followed by 35SO42- labeling for 6 hours. Labeled proteoglycans were precipitated using Alcian blue and measured in a raytest radio-TLC analyzer. The incubation with ***BMP*** -2 was defined to correlate the in-vivo stimulus meaning the operation. Results: The ***proteoglycan*** ***synthesis*** was significantly reduced by irradiation 1 hour before or 1 day after ***BMP*** -2 incubation, if the dosage was at Least 7 Gy. Higher doses than 7 Gy did not lead to lower proteoglycan levels. There was only a trend for a reduction of ***proteoglycan*** ***synthesis*** by 3 Gy irradiation, but no significant difference compared to the non-irradiated control. An irradiation 3 days after ***BMP*** -2 incubation had no effect on proteoglycan. Conclusion: A dose and time dependent effect of radiation on ***BMP*** -2-induced ***proteoglycan*** ***synthesis*** was observed. Therefore the results of clinical in-vivo studies were reproduced exactly by the limb bud test. We established an in-vitro cell model to analyze the mechanism of the prevention of heterotopic ossification by radiotherapy on cellular or sub-cellular level.

L6 ANSWER 38 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 22
AN 2000:424913 BIOSIS <<LOGINID::20071022>>
DN PREV200000424913
TI Hedgehog proteins stimulate chondrogenic cell differentiation and cartilage formation.
AU Enomoto-Iwamoto, Motomi; Nakamura, Takashi; Aikawa, Tomonao; Higuchi, Yoshinobu; Yuasa, Takahito; Yamaguchi, Akira; Nohno, Tsutomu; Noji, Sumihare; Matsuya, Tokuzo; Kurisu, Kojiro; Koyama, Eiki; Pacifici, Maurizio; Iwamoto, Masahiro [Reprint author]
CS Department of Oral Anatomy and Developmental Biology, Osaka University Faculty of Dentistry, 1-8 Yamadaoka, Suita, Osaka, 565-0871, Japan
SO Journal of Bone and Mineral Research, (September, 2000) Vol. 15, No. 9, pp. 1659-1668. print.
CODEN: JBMREJ. ISSN: 0884-0431.
DT Article
LA English
ED Entered STN: 4 Oct 2000
Last Updated on STN: 8 Jan 2002
AB Sonic hedgehog (Shh) and Indian hedgehog (Ihh) are important regulators of skeletogenesis, but their roles in this complex multistep process are not fully understood. Recent studies have suggested that the proteins participate in the differentiation of chondrogenic precursor cells into chondrocytes. In the present study, we have tested this possibility more directly. We found that implantation of dermal fibroblasts expressing hedgehog proteins into nude mice induces ectopic cartilage and bone formation. Immunohistological and reverse-transcription polymerase chain reaction (RT-PCR) analyses revealed that the ectopic tissues derived largely if not exclusively from host cells. We found also that treatment of clonal prechondrogenic RMD-1 and ATDC5 cells in culture with Ihh or recombinant amino half of Shh (recombinant N-terminal portion of Shh (rShh-N)) induced their differentiation into chondrocytes, as revealed by cytoarchitectural changes, Alcian blue staining and ***proteoglycan*** ***synthesis*** . Induction of RMD-1 cell differentiation by Ihh or rShh-N was synergistically enhanced by cotreatment with bone morphogenetic protein 2 (***BMP*** -2) but was blocked by cotreatment with fibroblast growth factor 2 (FGF-2). Our findings indicate that hedgehog proteins have the ability to promote differentiation of chondrogenic precursor cells and that their action this process can be influenced and modified by synergistic or antagonist cofactors.

L6 ANSWER 39 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 23
AN 2001:4431 BIOSIS <<LOGINID::20071022>>
DN PREV200100004431
TI Porcine fetal enamel matrix derivative stimulates proliferation but not differentiation of pre-osteoblastic 2T9 cells, inhibits proliferation and stimulates differentiation of osteoblast-like MG63 cells, and increases proliferation and differentiation of normal human osteoblast NHOst cells.
AU Schwartz, Z.; Carnes, D. L., Jr.; Pulliam, R.; Lohmann, C. H.; Sylvia, V. L.; Liu, Y.; Dean, D. D.; Cochran, D. L.; Boyan, B. D. [Reprint author]
CS Department of Orthopaedics, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX, 78229-3900, USA BoyanB@uthscsa.edu
SO Journal of Periodontology, (August, 2000) Vol. 71, No. 8, pp. 1287-1296. print.
CODEN: JOPRAJ. ISSN: 0022-3492.
DT Article
LA English
ED Entered STN: 21 Dec 2000
Last Updated on STN: 21 Dec 2000
AB Background: Embryonic enamel matrix proteins are hypothesized to be involved in the formation of acellular cementum during tooth development, suggesting that these proteins can be used to regenerate periodontal tissues. Enamel matrix protein derived from embryonic porcine tooth germs is used clinically, but the mechanisms by which it promotes the formation of cementum, periodontal ligament, and bone are not well understood. Methods: This study examined the response of osteoblasts at 3 stages of osteogenic maturation to porcine fetal enamel matrix derivative (EMD). Proliferation (cell number and (3H)-thymidine incorporation), differentiation (alkaline phosphatase and osteocalcin), matrix synthesis ((35S)-sulfate incorporation; percentage of collagen production), and local factor production (prostaglandin E2 (PGE2) and transforming growth factor-beta 1 (TGF-beta1)) were measured in cultures of 2T9 cells (pre-osteoblasts which exhibit osteogenesis in response to bone morphogenetic protein-2 (***BMP*** -2)), MG63 human osteoblast-like osteosarcoma cells, and normal human osteoblasts (NHOst cells). Results: EMD regulated osteoblast proliferation and differentiation, but the effects were cell-specific. In 2T9 cell cultures, EMD increased proliferation but had no effect on alkaline phosphatase-specific activity. EMD decreased proliferation of MG63 cells and increased cellular alkaline phosphatase and osteocalcin production. There was no effect on collagen ***synthesis*** , ***proteoglycan*** sulfation, or PGE2 ***production*** ; however, TGF-beta1 content of the conditioned media was increased. There was a 60-fold increase in cell number in third passage NHOst cells cultured for 35 days in the presence of EMD. EMD also caused a biphasic increase in alkaline phosphatase that was maximal at day 14. Conclusions: EMD affects early states of osteoblastic maturation by stimulating proliferation, but as cells mature in the lineage, EMD enhances differentiation.

L6 ANSWER 40 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 24
AN 2001:409765 BIOSIS <<LOGINID::20071022>>
DN PREV200100409765
TI Genetic enhancement of matrix synthesis by articular chondrocytes: Comparison of different growth factor genes in the presence and absence of interleukin-1.
AU Smith, P.; Shuler, F. D.; Georgescu, H. I.; Ghivizzani, S. C.; Johnstone, B.; Niyibizi, C.; Robbins, P. D.; Evans, C. H. [Reprint author]
CS Center for Molecular Orthopedics, Harvard Medical School, 221 Longwood Avenue, BL-152, Boston, MA, 02115, USA
SO Arthritis and Rheumatism, (May, 2000) Vol. 43, No. 5, pp. 1156-1164. print.
CODEN: ARHEAW. ISSN: 0004-3591.
DT Article
LA English
ED Entered STN: 29 Aug 2001
Last Updated on STN: 22 Feb 2002
AB Objective. To determine whether articular chondrocytes express growth factor genes delivered by adenoviral vectors and whether expression of these genes influences matrix synthesis in the presence and absence of interleukin-1 (IL-1). Methods. Monolayer cultures of rabbit articular chondrocytes were infected with recombinant adenovirus carrying genes encoding the following growth factors: insulin-like growth factor 1 (IGF-1), transforming growth factor beta1 (TGFbeta1), and bone morphogenetic protein 2 (***BMP*** -2). As a control, cells were transduced with the lac Z gene. Cultures were also treated with each growth factor supplied as a protein. Levels of gene expression were noted, and the ***synthesis*** of ***proteoglycan*** , collagen, and noncollagenous proteins was measured by radiolabeling. Collagen was typed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and autoradiography. The effects of growth factor gene transfer on ***proteoglycan*** ***synthesis*** in the presence of IL-1 were also measured. Results. The expression of all transgenes was high following adenoviral transduction. ***Proteoglycan*** ***synthesis*** was stimulated apprx8-fold by the ***BMP*** -2 gene and 2-3-fold by the IGF-1 gene. The effects of ***BMP*** -2 and IGF-1 genes were additive upon cotransduction. Synthesis of collagen and noncollagenous proteins, in contrast, was most strongly stimulated by the IGF-1 gene. In each case, collagen typing confirmed the synthesis of type II collagen. IL-1 suppressed ***proteoglycan*** ***synthesis*** by 50-60%. IGF-1 and TGFbeta genes restored ***proteoglycan*** ***synthesis*** to control levels in the presence of IL-1. The ***BMP*** -2 gene, in contrast, elevated ***proteoglycan*** ***synthesis*** beyond control levels in the presence of IL-1. Conclusion. Transfer of growth factor genes to articular chondrocytes can greatly increase matrix synthesis in vitro, even in the presence of the inflammatory cytokine IL-1. This result encourages the further development of gene therapy for the repair of damaged cartilage.

L6 ANSWER 41 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:140581 CAPLUS <<LOGINID::20071022>>
DN 134:276100
TI Extracellular matrix modulation of rhGDF-5 induced cellular differentiation
AU Heidaran, Mohammad A.; Daverman, Robin; Thompson, Andrea; Ng, Chee Keng;
Pohl, Jens; Poser, James W.; Spiro, Robert C.
CS Orquest, Inc., Mountain View, CA, USA

SO e-biomed [online computer file] (2000), 1, 121-135
CODEN: EBIOF4; ISSN: 1524-8909
URL: http://pinkerton.catchword.com/vl=80279380/cl=20/nw=1/fm=docpdf/rpsv/catchword/mal/15248909/v1n9/s21/p121.idx
PB Mary Ann Liebert, Inc.
DT Journal; (online computer file)
LA English
AB Growth and differentiation factor-5 (GDF-5) is a divergent member of the TGF-.beta./bone morphogenetic protein (***BMP***) superfamily that is required for proper skeletal patterning and joint development in the vertebrate limb. Based on the homol. of GDF-5 to other bone-inducing ***BMP*** family members, the inductive activity of a recombinant form of human GDF-5 (rhGDF-5), and the influence of the extracellular matrix (ECM) on this inductive activity was evaluated in a series of well-defined in vitro assays. Fetal rat calvarial (FRC) cells were plated on various purified extracellular matrix proteins in the presence of rhGDF-5 (100 ng/mL) for 3 wk and scored for differentiation at the level of morphol., overall ***proteoglycan*** ***synthesis*** and deposition, aggrecan and Type II collagen mRNA and protein expressions. Results show that GDF-5 stimulated chondrogenic nodule formation by FRC cells plated on Type I collagen but to a lesser extent on tissue culture plastic or fibronectin. These chondrogenic nodules stained heavily with Alcian blue and expressed chondrogenic markers such as Type II collagen and aggrecan, as judged by immunohistochem. and RT-PCR analyses, resp. Cells in the monolayer that surrounded the nodules did not express the chondrogenic markers. The mol. signaling mechanism by which GDF-5 induces chondrogenesis modulators of intracellular signaling mediators. Results show that the ligand-dependent chondrogenesis was inhibited by the calcium ionophore A23187, rapamycin but not by dibutyryl-cAMP, Na3/VO4, or EGTA. The known effects of A23187 and rapamycin on intracellular signaling pathway suggest that the GDF-5/Type I collagen-induced chondrogenesis is mediated through modulation of intracellular calcium concn. accompanied by activation of the p70 S6 kinase (p70s6k) signaling pathway. Together, these results indicate that cellular interaction with Type I collagen significantly enhances the differentiating activity of GDF-5. This effect is likely mediated by the convergence of downstream matrix and growth factor receptor signaling pathways.
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 42 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2000106705 EMBASE <<LOGINID::20071022>>
TI Role of nitric oxide in the inhibition of ***BMP*** -2-mediated stimulation of ***proteoglycan*** ***synthesis*** in articular cartilage.
AU Van Der Kraan P.M.; Vitters E.L.; Van Beuningen H.M.; Van De Loo F.A.J.; Van Den Berg W.B.
CS Dr. P.M. Van der Kraan, Department of Rheumatology, University Hospital Nijmegen, Geert Grooteplein 8, 6525 GA Nijmegen, Netherlands. P.vanderkraan@reuma.azn.nl
SO Osteoarthritis and Cartilage, (Mar 2000) Vol. 8, No. 2, pp. 82-86.
Refs: 21
ISSN: 1063-4584 CODEN: OSCAEO
CY United Kingdom
DT Journal; Article
FS 031 Arthritis and Rheumatism
LA English
SL English
ED Entered STN: 6 Apr 2000
Last Updated on STN: 6 Apr 2000
AB Objective: Bone morphogenetic protein-2 (***BMP*** -2)-mediated stimulation of articular cartilage ***proteoglycan*** (PG) ***synthesis*** is suppressed in arthritic murine knee joints and by interleukin-1 (IL-1). The goal of this study was to investigate whether the gaseous mediator nitric oxide (NO) plays a crucial role in the inhibition of ***BMP*** -2 effects by IL-1. Methods: Bone morphogenetic protein-2 alone or in combination with IL-1 was injected into the right knee joint of wild-type and NOS2 deficient C57Bl/6x129/Sv mice. ***Proteoglycan*** ***synthesis*** was measured ex vivo by incorporation of (35)S-sulfate on day 1, 2 and 3 after injection. To study the role of NO in the inhibition ***BMP*** -2- mediated stimulation of PG synthesis in arthritic joints, ***BMP*** -2 was injected intra-articularly in the joints of wild-type and NOS2 deficient mice with zymosan-induced arthritis. To check for NOS2 deficiency, NO production was measured in conditioned medium after challenge of patellae with surrounding tissue with IL-1. Results: ***BMP*** -2 potently stimulated ***proteoglycan*** ***synthesis*** in articular cartilage of normal knees (up to 4-fold) but not in arthritic knees. Co-injection of ***BMP*** -2 with tumor necrosis factor .alpha. had no effect on ***BMP*** -2-mediated stimulation of PG synthesis but co-injection with IL-1 .alpha. resulted in a nearly total inhibition of ***BMP*** -2-mediated stimulation. In contrast, in NOS2 deficient mice IL-1 had no effect on ***BMP*** -2-mediated stimulation of PG synthesis. However, injection of ***BMP*** -2 into arthritic knee joints of NOS2 knock out mice did not result in significant stimulation of PG synthesis. Conclusions: In this study we show that NO plays a role in the inhibition of ***BMP*** -2-mediated stimulation of PG synthesis by IL-1. However, NO, or at least NOS2, plays no dominant role in the inhibition of ***BMP*** -2 effects in arthritic knee joints. (C) 2000 OsteoArthritis Research Society International.

L6 ANSWER 43 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 1999423225 EMBASE <<LOGINID::20071022>>
TI Age-dependent effects of hedgehog protein on chondrocytes.
AU Iwasaki M.; Jikko A.; Le A.X.
CS Dr. M. Iwasaki, Department of Orthopaedic Surgery, Osaka Rosai Hospital, 1179-3 Nagasone-cho, Sakai, Osaka 591, Japan
SO Journal of Bone and Joint Surgery - Series B, (Nov 1999) Vol. 81, No. 6, pp. 1076-1082.
Refs: 36
ISSN: 0301-620X CODEN: JBSUAK
CY United Kingdom
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry
033 Orthopedic Surgery
LA English
SL English
ED Entered STN: 29 Dec 1999
Last Updated on STN: 29 Dec 1999
AB One morphogenetic protein (***BMP***) has a crucial role in osteochondrogenesis of bone formation as well as in the repair of fractures. The interaction between hedgehog protein and BMPs is inferred from recent molecular studies. Hedgehog genes encode secreted proteins which mediate patterning and growth during skeletal development. We have shown that Indian hedgehog gene (Ihh) is expressed in cartilage anlage and later in mature and hypertrophic chondrocytes. This finding suggests that Ihh may regulate the development of chondrocytes. Our results in this study have shown that Ihh transcripts were expressed in hypertrophic chondrocytes in mice at three days but not at three weeks, although a similar expression pattern of .alpha.1 (X) collagen could be observed in both types of cartilage. To investigate the possibility that there are direct and age-dependent functions of Ihh in chondrocytes, cultured chondrocytes were treated with the amino-terminal fragment of Sonic hedgehog protein (Shh-N) which can functionally substitute for Ihh protein. Shh-N did not affect the proliferation and differentiation of chondrocytes from three-week-old mice but had a significant effect on three-day-old mice. It enhanced proliferation up to 128% of the control culture in a dose-dependent manner. Although there was no effect in Shh-N-treated cultures, Shh-N enhanced the stimulatory effect of parathyroid hormone (PTH) on the synthesis of proteoglycans. Because the effects of Shh-N on chondrocyte differentiation in this culture system differed from those of bone morphogenetic protein-2 (BMP2) and PTH, in terms of ***proteoglycan*** ***synthesis*** and ALPase activity, it is unlikely that BMP2 or PTH/PTH-related protein mediates the direct effects of Ihh in chondrocytes. Our study shows that Ihh can function in chondrocytes in a direct and age-dependent fashion.

L6 ANSWER 44 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 25
AN 1998:476158 BIOSIS <<LOGINID::20071022>>
DN PREV199800476158
TI Regulation of BMP7 expression during kidney development.
AU Godin, Robert E.; Takaesu, Norma T.; Robertson, Elizabeth J. [Reprint author]; Dudley, Andrew T.
CS Dep. Molecular Cellular Biol., Harvard Univ., 16 Divinity Ave., Cambridge, MA 02138, USA
SO Development (Cambridge), (Sept., 1998) Vol. 125, No. 17, pp. 3473-3482. print.
CODEN: DEVPED. ISSN: 0950-1991.
DT Article
LA English
ED Entered STN: 5 Nov 1998
Last Updated on STN: 5 Nov 1998
AB Members of the Bone Morphogenetic Protein (***BMP***) family exhibit overlapping and dynamic expression patterns throughout embryogenesis. However, little is known about the upstream regulators of these important signaling molecules. There is some evidence that ***BMP*** signaling may be autoregulative as demonstrated for BMP4 during tooth development. Analysis of BMP7 expression during kidney development, in conjunction with studies analyzing the effect of recombinant BMP7 on isolated kidney mesenchyme, suggest that a similar mechanism may operate for BMP7. We have generated a beta-gal-expressing reporter allele at the BMP7 locus to closely monitor expression of BMP7 during embryonic kidney development. In contrast to other studies, our analysis of BMP7/lacZ homozygous mutant embryos, shows that BMP7 expression is not subject to autoregulation in any tissue. In addition, we have used this reporter allele to analyze the expression of BMP7 in response to several known survival factors (EGF, bFGF) and inducers of metanephric mesenchyme, including the ureteric bud, spinal cord and LiCl. These studies show that treatment of isolated mesenchyme with EGF or bFGF allows survival of the mesenchyme but neither factor is sufficient to maintain BMP7 expression in this population of cells. Rather, BMP7 expression in the mesenchyme is contingent on an inductive signal. Thus, the reporter allele provides a convenient marker for the induced mesenchyme. Interestingly LiCl has been shown to activate the Wnt signaling pathway, suggesting that BMP7 expression in the mesenchyme is regulated by a Wnt signal. Treatment of whole kidneys with sodium chlorate to disrupt ***proteoglycan*** ***synthesis*** results in the loss of BMP7 expression in the mesenchyme whereas expression in the epithelial components of the kidney are unaffected. Heterologous recombinations of ureteric bud with either limb or lung mesenchyme demonstrate that expression of BMP7 is maintained in this epithelial structure. Taken together, these data indicate that BMP7

expression in the epithelial components of the kidney is not dependent on cell-cell or cell-ECM interactions with the metanephric mesenchyme. By contrast, BMP7 expression in the metanephric mesenchyme is dependent on proteoglycans and possibly Wnt signaling.

L6 ANSWER 45 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 26
AN 1998:176156 BIOSIS <<LOGINID::20071022>>
DN PREV199800176156
TI Cartilage-derived morphogenetic proteins and osteogenic protein-1 differentially regulate osteogenesis.
AU Erlacher, Ludwig; McCartney, John; Piek, Ester; Ten Dijke, Peter; Yanagishita, Masaki; Oppermann, Hermann; Luyten, Frank P. [Reprint author]
CS Div. Rheumatol., UZ Pellenberg, Weligerveld 1, 3212 Pellenberg, Belgium
SO Journal of Bone and Mineral Research, (March, 1998) Vol. 13, No. 3, pp. 383-392. print.
CODEN: JBMREJ. ISSN: 0884-0431.
DT Article
LA English
ED Entered STN: 20 Apr 1998
Last Updated on STN: 20 Apr 1998
AB Cartilage-derived morphogenetic proteins-1 and -2 (CDMP-1 and CDMP-2) are members of the bone morphogenetic protein (***BMP***) family, which play important roles in embryonic skeletal development. We studied the biological activities of recombinant CDMP-1 and CDMP-2 in chondrogenic and osteogenic differentiation and investigated their binding properties to type I and type II serine/threonine kinase receptors. In vivo, CDMP-1 and CDMP-2 were capable of inducing dose-dependently de novo cartilage and bone formation in an ectopic implantation assay. In vitro studies using primary chondrocyte cultures showed that both CDMP-1 and CDMP-2 stimulated equally de novo ***synthesis*** of ***proteoglycan*** aggrecan in a concentration-dependent manner. This activity was equipotent when compared with osteogenic protein-1 (OP-1). In contrast, CDMPs were less stimulatory than OP-1 in osteogenic differentiation as evaluated by alkaline phosphatase activity and expression levels of bone markers in ATDC5, ROB-C26, and MC3T3-E1 cells. CDMP-2 was the least osteogenic in these assays. Receptor binding studies of CDMP-1 and CDMP-2 revealed that both have affinity for the ***BMP*** receptor type IB (BMPR-IB) and BMPR-II, and weakly for BMPR-IA. Moreover, using a promoter/reporter construct, transcriptional activation signal was transduced by BMPR-IB in the presence of BMPR-II upon CDMP-1 and CDMP-2 binding. Our data show that distinct members of the ***BMP*** family differentially regulate the progression in the osteogenic lineage, and this may be due to their selective affinity for specific receptor complexes.

L6 ANSWER 46 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 1998297301 EMBASE <<LOGINID::20071022>>
TI Differential effects of local application of ***BMP*** -2 or TGF-.beta.1 on both articular cartilage composition and osteophyte formation.
AU Van Beuningen H.M.; Glansbeek H.L.; Van Der Kraan P.M.; Van Den Berg W.B.
CS Dr. H.M. Van Beuningen, Department of Rheumatology, University Hospital Nijmegen, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, Netherlands. h.vanbeuningen@reuma.azn.nl
SO Osteoarthritis and Cartilage, (Sep 1998) Vol. 6, No. 5, pp. 306-317.
Refs: 40
ISSN: 1063-4584 CODEN: OSCAEO
CY United Kingdom
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry
033 Orthopedic Surgery
LA English
SL English
ED Entered STN: 15 Oct 1998
Last Updated on STN: 15 Oct 1998
AB Objective: The related molecules bone morphogenetic protein-2 (***BMP*** -2) and transforming growth factor beta-1 (TGF-.beta.1) have both been shown to stimulate chondrocyte ***proteoglycan*** (PG) ***synthesis*** in vitro. We investigated the in-vivo effects of these factors on articular cartilage PG metabolism. Design: Several doses of ***BMP*** -2 or TGF-.beta.1 were injected into the murine knee joint, once or repeatedly. Patellar cartilage PG synthesis was measured by [(35)S]-sulfate incorporation and reverse transcriptase polymerase chain reaction (RT-PCR). PG content was analyzed by measuring safranin O staining intensity on histologic sections. Results: A single injection of 200 ng ***BMP*** - 2 induced a much earlier and more impressive stimulation of articular cartilage PG synthesis, than 200 ng TGF-.beta.1. RT-PCR revealed that both factors upregulated mRNA of aggrecan more than that of biglycan and decorin. However, 21 days after a single injection of 200 ng TGF-.beta.1 PG synthesis still was significantly increased, while stimulation by ***BMP*** -2 only lasted for 3 to 4 days. Stimulation by ***BMP*** -2 could be prolonged to at least 2 weeks by triple injections of 200 ng each, at alternate days. Remarkably, even after this intense exposure to ***BMP*** -2, stimulation of PG synthesis was not reflected in long-lasting enhancement of PG content of articular cartilage. In contrast, even a single injection with 200 ng of TGF-.beta.1 induced prolonged enhancement of PG content. After repeated injections, both ***BMP*** -2 and TGF-.beta.1 induced chondrogenesis at specific sites. 'Chondrophytes' induced by ***BMP*** -2 were found predominantly in the region where the growth plates meet the joint space, while those triggered by TGF-.beta.1 originated from the periosteum also at sites remote from the growth plates. Conclusions: ***BMP*** -2 and TGF-.beta. stimulate PG synthesis and PG content with different kinetics, and these factors have different chondro-inductive properties.

L6 ANSWER 47 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 1997227178 EMBASE <<LOGINID::20071022>>
TI Characterization of epiphycan, a small proteoglycan with a leucine-rich repeat core protein.
AU Johnson H.J.; Rosenberg L.; Choi H.U.; Garza S.; Hook M.; Neame P.J.
CS P.J. Neame, Shriners Hospital for Children, 12502 N. Pine Dr., Tampa, FL 33612, United States. pneame@com1.med.usf.edu
SO Journal of Biological Chemistry, (1997) Vol. 272, No. 30, pp. 18709-18717.
Refs: 26
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry
LA English
SL English
ED Entered STN: 4 Sep 1997
Last Updated on STN: 4 Sep 1997
AB The epiphysis of developing bones is a cartilaginous structure that is eventually replaced by bone during skeletal maturation. We have separated a dermatan sulfate proteoglycan, epiphycan, from decorin and biglycan by using dissociative extraction of bovine fetal epiphyseal cartilage, followed by sequential ion-exchange, gel permeation, hydrophobic, and Zn(2+) chelate chromatographic steps. Epiphycan is a member of the small leucine-rich proteoglycan family, contains seven leucine-rich repeats (LRRs), is related to osteoglycin (***osteoinductive*** factor) (Bentz, H., Nathan, R. M., Rosen, D. M., Armstrong, R. M., Thompson, A. Y., Segarini, P. R., Mathews, M. C., Dasch, J., Piez, K. A., and Seyedin, S. M. (1989) J. Biol. Chem. 264, 20805- 20810), and appears to be the bovine equivalent of the chick proteoglycan PG- Lb (Shinomura, T., and Kimata, K. (1992) J. Biol. Chem. 267, 1265-1270). The intact proteoglycan had a median size of 133 kDa. The core protein was 46 kDa by electrophoretic analysis, had a calculated size of 34,271 Da, and had two approximately equimolar N termini (APTLES... and ETYDAT...) separated by 11 amino acids. There were at least three O-linked oligosaccharides in the N- terminal region of the protein, based on blank cycles in Edman degradation and corresponding serine or threonine residues in the translated cDNA sequence. The glycosaminoglycans ranged in size from 23 to 34 kDa were more heterogeneous than those in other dermatan sulfate small leucine-rich proteoglycans and were found in the acidic N-terminal region of the protein core, N-terminal to the LRRs. A four-cysteine cluster was present at the N terminus of the LRRs, and a disulfide-bonded cysteine pair was present at the C terminus of the protein core. The seventh LRR and an N-linked oligosaccharide were between the two C-terminal cysteines. An additional potential N-glycosylation site near the C terminus did not appear to be substituted at a significant level.

L6 ANSWER 48 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 27
AN 1997:314919 BIOSIS <<LOGINID::20071022>>
DN PREV199799605407
TI Bone morphogenetic protein 2 stimulates articular cartilage ***proteoglycan*** ***synthesis*** in vivo but does not counteract interleukin-1-alpha effects on ***proteoglycan*** ***synthesis*** and content.
AU Glansbeek, Harrie L. [Reprint author]; Van Beuningen, Henk M.; Vitters, Elly L.; Morris, Elisabeth A.; Van Der Kraan, Peter M.; Van Den Berg, Wim B.
CS Dep. Rheumatol., University Hosp. Nijmegen, Geert Grooteplein zuid 8, 6525 GA Nijmegen, Netherlands
SO Arthritis and Rheumatism, (1997) Vol. 40, No. 6, pp. 1020-1028.
CODEN: ARHEAW. ISSN: 0004-3591.
DT Article
LA English
ED Entered STN: 26 Jul 1997
Last Updated on STN: 26 Jul 1997
AB Objective. To study the effect of bone morphogenetic protein 2 (***BMP*** -2) on articular cartilage ***proteoglycan*** (PG) ***synthesis*** in vivo and to investigate whether ***BMP*** -2 is able to counteract the effects of interleukin-1 (IL-1) on articular cartilage PG synthesis and content. Methods. ***BMP*** -2 alone or in combination with IL-1-alpha was injected into murine knee joints. PG synthesis was measured by 35S-sulfate incorporation using an ex vivo method or autoradiography. Cartilage PG content was analyzed by measuring Safranin O staining intensity on histologic sections. Results. ***BMP*** -2 appeared to be a potent stimulator of articular cartilage PG synthesis in vivo. However, ***BMP*** -2 was not able to counteract the deleterious effects of IL-1-alpha on articular cartilage PG synthesis and content. In addition, intraarticular injections of ***BMP*** -2 induced chondrophytes. Conclusion. Although ***BMP*** -2 is a very potent stimulator of cartilage PG synthesis in vivo, the therapeutic applications of ***BMP*** -2 are limited due to the inability of ***BMP*** -2 to counteract the effects of IL-1 and the induction of chondrophytes.

L6 ANSWER 49 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 28
AN 1997:483082 BIOSIS <<LOGINID::20071022>>
DN PREV199799782285
TI Cloning and characterization of the 5'-flanking region of the mouse diastrophic dysplasia sulfate transporter gene.
AU Kobayashi, Tatsuya [Reprint author]; Sugimoto, Toshitsugu; Saijoh, Kiyofumi; Fujii, Motoko; Chihara, Kazuo
CS Third Div., Dep. Med., Kobe Univ. Sch. Med., 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650, Japan
SO Biochemical and Biophysical Research Communications, (1997) Vol. 238, No. 3, pp. 738-743.
CODEN: BBRCA9. ISSN: 0006-291X.
DT Article
LA English
ED Entered STN: 7 Nov 1997
Last Updated on STN: 7 Nov 1997
AB Dyastrophic dysplasia sulfate transporter (DTDST) plays an important role in ***proteoglycan*** ***synthesis*** in the extracellular matrix of bone and cartilage. Recently, we found that the mouse DTDST gene was induced in pluripotent C3H10T1/2 cells during differentiation by bone morphogenetic protein-2 (***BMP*** -2). To clarify the transcriptional regulation of the DTDST gene, we have cloned the 5'-flanking region of the mouse DTDST gene by the PCR based gene walking method. Sequence analysis
revealed the presence of the TATA box followed by GC rich sequences containing two Sp-1 binding sites and a CBFA1 binding site. Transient transfection assays demonstrated that the basal transcriptional activity in osteoblastic MC3T3-E1 cells was mainly present between -309 and -275 bp upstream of the transcription start site (Segment -309/-275) which contained the consensus sequence for the xenobiotic-responsible element (XRE). Nuclear proteins from MC3T3-E1 cells and C3H10T1/2 cells could bind to this short segment in vitro. ***BMP*** -2 increased the promoter activity as well as the nuclear protein binding to the sequence in C3H10T1/2 cells. The present data suggest that the DTDST gene expression in osteoblasts and differentiating precursor cells to osteoblast/chondrocyte lineage would be mainly regulated by undetermined XRE binding transcription factors.

L6 ANSWER 50 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 29
AN 1996:215623 BIOSIS <<LOGINID::20071022>>
DN PREV199698771752
TI Human bone morphogenetic protein 2 contains a heparin-binding site which modifies its biological activity.
AU Ruppert, Rainer; Hoffmann, Elke; Sebald, Walter [Reprint author]
CS Physiol. Chem. II, Theodor-Boveri-Inst. Biowissenschaften der Univ., Am Hubland, D-97074 Wuerzburg, Germany
SO European Journal of Biochemistry, (1996) Vol. 237, No. 1, pp. 295-302.
CODEN: EJBCAI. ISSN: 0014-2956.
DT Article
LA English
ED Entered STN: 8 May 1996
Last Updated on STN: 8 May 1996
AB Bone morphogenetic protein 2 (***BMP*** -2) plays a decisive role during bone regeneration and repair as well as during various stages of embryonal development. A cDNA encoding mature human ***BMP*** -2 could be efficiently expressed in Escherichia coli, and after renaturation a dimeric ***BMP*** -2 protein of M-r 26000 was prepared with a purity greater 98%. The recombinant ***BMP*** -2 was functionally active as demonstrated by the induction of alkaline phosphatase activity in the C3H10T1/2 fibroblast cell line (EC-50 of 70 nM) and ***proteoglycan*** ***synthesis*** in embryonic chicken limb bud cells (EC-50) of 15-20 nM). A peptide 1-17 representing the N-terminal basic part of ***BMP*** -2 as well as heparin increased the specific activity of the protein about fivefold in the limb bud assay. These observations suggested that the N-termini reduce the specific activity of ***BMP*** -2, probably by interacting with heparinic sites in the extracellular matrix. This conclusion was supported by a variant EHBMP-2, where the N-terminal residues 1-12 of ***BMP*** -2 had been substituted by a dummy sequence of equal length and which showed an EC-50 value of around 1 nM which was affected neither by heparin nor by peptide 1-17. A physical interaction between ***BMP*** -2 and heparin could be seen in biosensor experiments, where ***BMP*** -2 bound to immobilized heparin with a dissociation constant, K-d, of approximately 20 nM, whereas the heparin-binding of variant EHBMP-2 was negligible. These results identify the basic N-terminal domains of dimeric ***BMP*** -2 as heparin-binding sites that are not obligatory for receptor activation but modulate its biological activity.

L6 ANSWER 51 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN
AN 1996:54119 BIOSIS <<LOGINID::20071022>>
DN PREV199698626254
TI Bone morphogenetic protein-2 (***BMP*** -2) maintains the phenotype of articular chondrocytes in long term monolayer culture.
AU Sailor, L. Zenzius; Wang, J. H.; Morris, E.; Hewick, R. M.
CS Genet. Inst., Cambridge, MA 02140, USA
SO Molecular Biology of the Cell, (1995) Vol. 6, No. SUPPL., pp. 391A.
Meeting Info.: Thirty-fifth Annual Meeting of the American Society for Cell Biology. Washington, D.C., USA. December 9-13, 1995.
CODEN: MBCEEV. ISSN: 1059-1524.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 2 Feb 1996
Last Updated on STN: 2 Feb 1996

L6 ANSWER 52 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 1994054142 EMBASE <<LOGINID::20071022>>
TI In vitro ***proteoglycan*** ***synthesis*** in response to extracts of demineralized bone.
AU Nathanson M.A.
CS Dr. M.A. Nathanson, Department of Anatomy, New Jersey Medical School, Newark, NJ 07103, United States
SO Clinical Orthopaedics and Related Research, (1994) No. 299, pp. 263-281.
ISSN: 0009-921X CODEN: CORTBR
CY United States
DT Journal; Article
FS 001 Anatomy, Anthropology, Embryology and Histology
021 Developmental Biology and Teratology
033 Orthopedic Surgery
LA English
SL English
ED Entered STN: 13 Mar 1994
Last Updated on STN: 13 Mar 1994
AB Two extracts of bovine bone, bone morphogenetic protein (***BMP***) supplied by the UCLA Bone Research Laboratory, and osteogenic factor extract (OFE) supplied by the industrial group Celtrix Pharmaceuticals, were tested for the ability to transform embryonic skeletal muscle into cartilage. Skeletal muscle was placed into organ cultures on substrata of Type I collagen and fed with concentrations of the extracts that their originators reported to be effective; however, only ***BMP*** was capable of eliciting the morphologic differentiation of cartilage. In contrast, both extracts supported patterns of glycosaminoglycan synthesis that mimicked the biochemical differentiation of cartilage-type extracellular matrix. Bone morphogenetic protein differed from OFE in its ability to elicit high levels of hyaluronic acid synthesis, although ***BMP*** and OFE upregulated synthesis of hyaluronic acid that was of sufficient chain length to support proteoglycan aggregate formation. Proteoglycan extracts of the cell layer and medium demonstrated that most of the ***proteoglycan*** ***synthesized*** in response to ***BMP*** was an aggrecan-like material, which was lost to the medium. That which synthesized in response to OFE was a proteoglycan with short glycosaminoglycan chains that had only a limited ability to aggregate. These results demonstrate that ***BMP*** is effective in promoting chondrogenesis by virtue of its ability to promote the synthesis of hyaluronic acid, and aggrecan, but suggests that other accessory matrix components must also be synthesized to anchor aggrecan in the cell layer. The ability to stimulate the synthesis of these other components may be lost on purification of ***BMP*** . Consequently, ***BMP*** may initiate several activities that collectively upregulate chondrogenesis and the production of cartilage extracellular matrix.

L6 ANSWER 53 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 30
AN 1994:154635 BIOSIS <<LOGINID::20071022>>
DN PREV199497167635
TI Recombinant bone morphogenetic protein-4, transforming growth factor-beta-1, and activin A enhance the cartilage phenotype of articular chondrocytes in vitro.
AU Luyten, Frank P. [Reprint author]; Chen, Ping; Paralkar, Vishwas; Reddi, A. H.
CS Bone Res. Branch, Building 10, Room 1N108, National Inst. Dental Res., National Inst. Health, Bethesda, MD 20892, USA
SO Experimental Cell Research, (1994) Vol. 210, No. 2, pp. 224-229.
CODEN: ECREAL. ISSN: 0014-4827.
DT Article
LA English
ED Entered STN: 8 Apr 1994
Last Updated on STN: 10 Apr 1994
AB Bone morphogenetic protein-4 (***BMP*** -4) is a member of the transforming growth factor-beta (TGF-beta) supergene family and is characterized by its ability to induce singly de novo cartilage and bone in vivo. The influence of recombinant bone morphogenetic protein-4 and some related members, TGF-beta-1 activin A, and inhibin A, on articular chondrocyte metabolism in the presence and absence of extracellular matrix has been examined. ***BMP*** -4 and TGF-beta-1 stimulated (35S)-sulfate incorporation in a dose-dependent manner in short-term monolayer, micromass, and explant cultures. Activin A showed a slight but significant stimulation of ***proteoglycan*** ***synthesis*** while inhibin A decreased metabolic activity. The effects observed were most pronounced in the explant culture system. Although the relative influence of the growth factors was less apparent in chondrocytes isolated from adult cartilage, the qualitative responses were similar with cells obtained from young animals. The maintenance and enhancement of the cartilage phenotype was further investigated by Northern blot analysis. ***BMP*** -4 and TGF-beta-1, increased the levels of expression of type II collagen and proteoglycan aggrecan in short-term cultures, while activin A and inhibin A did not affect these parameters significantly when

compared to serum-free control cultures. Binding experiments with 125I-***BMP*** -4, revealed the presence of specific, high-affinity binding sites with an apparent dissociation constant of 110 pM and about 6000 receptors per cell. Chemical cross-linking showed the presence of three components (apparent size 200, 90, and 70 kDa), demonstrating the presence of functional receptors for ***BMP*** -4 on primary articular chondrocytes.

L6 ANSWER 54 OF 56 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 31
AN 1992:185314 BIOSIS <<LOGINID::20071022>>
DN PREV199293096264; BA93:96264
TI NATURAL BOVINE OSTEOGENIN AND RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN-2B ARE EQUIPOTENT IN THE MAINTENANCE OF PROTEOGLYCANS IN BOVINE ARTICULAR CARTILAGE EXPLANT CULTURES.
AU LUYTEN F P [Reprint author]; YU Y M; YANAGISHITA M; VUKICEVIC S; HAMMONDS R G; REDDI A H
CS NATIONAL INST DENTAL RES, BUILDING 30, RM 211, NATIONAL INST HEALTH, BETHESDA MD 20892, USA
SO Journal of Biological Chemistry, (1992) Vol. 267, No. 6, pp. 3691-3695. CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 13 Apr 1992
Last Updated on STN: 13 Apr 1992
AB Osteogenin and related bone morphogenetic proteins are members of the transforming growth factor-.beta. superfamily, and were isolated by their ability to induce cartilage and bone formation in vivo. The influence of osteogenin, purified from bovine bone, and of recombinant human bone morphogenetic protein-2B (***BMP*** -2B) has been examined in bovine articular cartilage explants. Both differentiation factors stimulated in a dose-dependent manner the synthesis of proteoglycans and decreased their rate of degradation. At a dose of 30 ng/ml, ***proteoglycan*** ***synthesis*** was increased to levels observed with either 20 ng/ml insulin-like growth factor I, 10 ng/ml transforming growth factor-.beta., or 20% fetal bovine serum. This increase of biosynthetic rates above basal medium levels was observed in young, adolescent, and adult tissues. Analysis of the size of the newly synthesized proteoglycans, the glycosaminoglycan chain size, and the glycosaminoglycan type of explants treated with osteogenin or ***BMP*** -2B were very comparable to each other, and to proteoglycans isolated from cartilage treated with either insulin-like growth factor I or fetal bovine serum. These results demonstrate that osteogenin and ***BMP*** -2B alone are capable of stimulating and maintaining the chondrocyte phenotype in vitro.

L6 ANSWER 55 OF 56 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 1992080363 EMBASE <<LOGINID::20071022>>
TI Proteoglycan-Lb, a small dermatan sulfate proteoglycan expressed in embryonic chick epiphyseal cartilage, is structurally related to ***osteoinductive*** factor.
AU Shinomura T.; Kimata K.
CS K. Kimata, Inst. for Molec. Sci. of Med., Aichi Medical University, Nagakute, Aichi 480-11, Japan
SO Journal of Biological Chemistry, (1992) Vol. 267, No. 2, pp. 1265-1270. ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 029 Clinical and Experimental Biochemistry
LA English
SL English
ED Entered STN: 17 Apr 1992
Last Updated on STN: 17 Apr 1992
AB We have isolated cDNA clones encoding the core protein of PG-Lb, proteoglycan which has been shown to be preferentially expressed in the zone of flattened chondrocytes of the developing chick limb cartilage (Shinomura, T., Kimata, K., Oike, Y., Yano, S., and Suzuki, S. (1984) Dev. Biol. 103, 211-220). The deduced amino acid sequence from the cDNA analysis indicates the presence of consensus leucine-rich repeats which are present in other small proteoglycans, decorin, biglycan, and fibromodulin. However, the homology analysis revealed that chick PG-Lb showed a higher homology (about 50% in the region containing leucine-rich repeats) to human ***osteoinductive*** factor, OIF, rather than to the other small proteoglycans. Furthermore, 6 cysteine residues are detected in both PG-Lb and OIF with invariant relative positions. Therefore, such an evolutionarily conserved structure in the PG-Lb core protein might be involved in some important biological functions of this molecule. In close relation to the structural similarity to OIF, the unique expression of PG-Lb in the ossifying area of cartilage suggested the possible participation of this proteoglycan in osteogenic processes.

L6 ANSWER 56 OF 56 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1991:529120 CAPLUS <<LOGINID::20071022>>
DN 115:129120
TI Xenopus laevis bone morphogenetic protein genes and their recombinant expression
IN Murakami, Kazuo; Ueno, Naoto; Kato, Yukio
PA Takeda Chemical Industries, Ltd., Japan; Scitech Research Co., Ltd.
SO Eur. Pat. Appl., 28 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 416578	A2	19910313	EP 1990-117079	19900905
EP 416578	A3	19920422		
EP 416578	B1	19960731		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2024629	A1	19910307	CA 1990-2024629	19900905
CA 2024629	C	20010724		
JP 04154799	A	19920527	JP 1990-235405	19900905
JP 3045398	B2	20000529		
AT 140965	T	19960815	AT 1990-117079	19900905
US 5453419	A	19950926	US 1993-56564	19930430
US 5670338	A	19970923	US 1995-455550	19950531
PRAI JP 1989-229250	A	19890906		
JP 1990-190774	A	19900720		
US 1990-577892	B1	19900905		
US 1993-56564	A3	19930430		

AB Genes encoding Xenopus laevis bone morphogenetic proteins (***BMP***) are cloned in Escherichia coli and expressed in COS cells. These proteins can be used for promoting the ***synthesis*** of ***proteoglycan*** in cartilage cells in mammals. The genes encoding ***BMP*** -A4, A5, B9, C4, and M3 were cloned from a X. laevis liver chromosomal DNA library using rat actin .beta.A cDNA as a probe. The genes encoding BMP1-A, BMP2B, and Vgr-1 were cloned from an egg chromosomal DNA library and expressed in COS cells. The recombinant products promoted the ***synthesis*** of ***proteoglycan*** by cultured rat chondrocytes.

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